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# Application of Pd-Catalyzed Cross-Coupling Reactions in the Synthesis of 5,5-Dimethyl-5,6-dihydro-4-*H*-pyrrolo[1,2-*b*]pyrazoles that inhibit ALK5 Kinase

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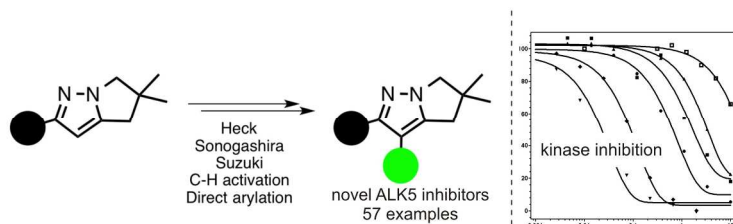
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Application of Pd-Catalyzed Cross-Coupling Reactions in the Synthesis of 5,5-Dimethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazoles that inhibit ALK5 Kinase

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**ABSTRACT:** C-H activation of position 3 of a substituted pyrazole ring catalyzed by palladium(II) was straightforward and convenient for arylated or heteroarylated 5,5-dimethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazoles. Moreover, we introduced simple protection of the nitrogen in the pyridin-2-yl directing group, which otherwise does not allow cross-coupling reaction, by transformation to the *N*-oxide. Selected final products were reasonably selective ALK5 kinase inhibitors.

## Introduction

The development of new synthetic strategies for molecular construction by organic chemists has always been challenging and the improved production of complex molecules from simple, nontoxic and economically available starting materials is always desirable. In today's chemistry, the cross-coupling reaction is among the most employed strategies of every synthetic lab and C–H activation/functionalization process appears to be a wonderful synthetic tool for molecular derivatizations.<sup>1</sup> The main disadvantage of this method compared to classical cross-coupling reactions is a requisite directing group at the appropriate position, which is often unwanted in the final product. The solution is the direct functionalization of a C–H bond which is an ever-growing area of interest.<sup>2</sup> The atom economy and fast accessibility of the desired and often biologically active products make these reactions really attractive.

In the past, we developed a convenient synthetic protocol for molecules containing a 5,5-dimethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (DPP) core containing various substituents via protected hydrazone **1** formation / homoallenyl azine **2** generation / thermal intramolecular cycloaddition reaction cascade leading to DPP **3** heterocycles (Experimental Section).<sup>3</sup> This structural motif appears in several compounds with attractive biological activities, e.g. plant alkaloid withasomnine<sup>4</sup>, synthetic  $\beta$ 3 adrenergic receptor agonists and kinase inhibitors,<sup>5</sup> including galunisertib (LY2157299), a drug that is currently under clinical investigation in cancer patients (Figure 1).<sup>6</sup> Galunisertib has been developed as an inhibitor of transforming growth factor- $\beta$  (TGF- $\beta$ ) type I receptor kinase (TGFB1, also known as ALK5).<sup>5f-i,6</sup> Binding of TGF- $\beta$  to this transmembrane

receptor enables its kinase activity leading to highly complex intracellular signalling pathway regulating proliferation, differentiation, migration, extracellular matrix production and apoptosis.<sup>7</sup> Due to known deregulation of TGF- $\beta$  signalling in several diseases, ALK5 and other components of the pathway have been studied as possible drug targets for different therapeutic uses.<sup>6,7b</sup>

These findings and a longstanding interest in the preparation of DPPs in our laboratory led us to investigate the reactivity of such a core more thoroughly as means to find biologically active products. Thus, we applied various Pd-catalyzed transformations on synthesized derivatives **3a-e** (Experimental Section) facilitating fast accessibility of structurally enriched products.

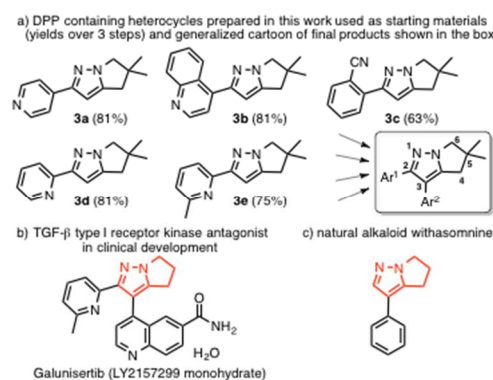
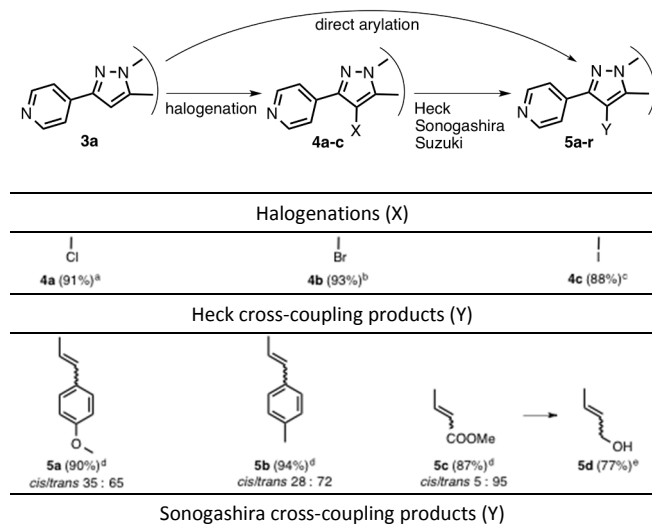


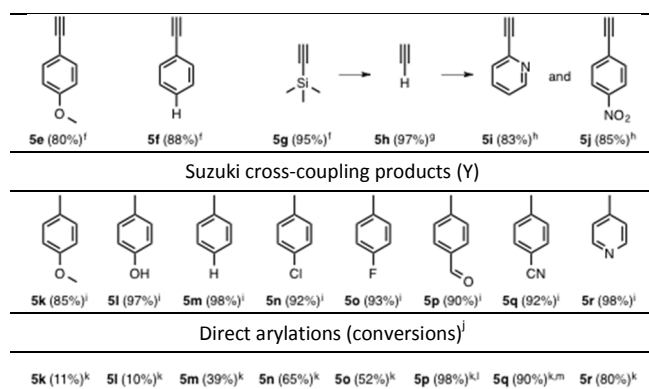
Figure 1. Synthesized DPPs **3a-e** as a starting material and two examples of bioactive compounds containing the respective core

## Results and Discussion

We divided the study into two parts depending on the position of nitrogen atom bound to the side aromatic substituent at C2, the pyridin-2-yl and pyridin-4-yl moieties. We explored the reactivity of latter DPPs first (Scheme 1) and applied this chemistry further to pyridin-2-yl derivatives, which are known to be biologically more potent.<sup>5,6</sup> We synthesized chloro, bromo and iodo compounds **4a-c** and then applied Heck (**5a-d**), Sonogashira (**5e-j**) and Suzuki (**5k-r**) cross-coupling reaction protocols. In general, all reactions we carried out afforded good to high yields. However, direct arylation clearly showed feasibility only for electron-deficient aryl bromides whereas electron-rich counterparts revealed negligible conversions (Scheme 1). Using the data resulting from preliminary biological testing we selected the most promising compounds and prepared relevant structures bearing quinolin-4-yl (**3b**) and 2-cyanophenyl (**3c**) substitutions at C2 (Experimental Section).

Scheme 1. Transformations at C3 on derivative **3a**





a) NCS, anh.  $\text{CHCl}_3$ , rt, 18 h; b) NBS, anh.  $\text{CHCl}_3$ , rt, 0.5 h; c) NIS, anh.  $\text{CHCl}_3/\text{MeCN}$ , rt to 60 °C, 23 h; d) **4b**, substituted alkene,  $\text{Pd}(\text{dba})_2$ ,  $\text{P}(t\text{-Bu})_3$ ,  $\text{Et}_3\text{N}$ , DMF, 100 °C, 2-8 h; e) 1 M DIBAL-H/DCM, 0 °C, 1 h; f) **4c**, substituted acetylene,  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ , CuI, MeCN, 70 °C, 1 h; g)  $\text{K}_2\text{CO}_3$ , MeOH, rt, 0.5 h; h) aryl iodide,  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ , CuI, MeCN, 70 °C, 1 h; i) **4b**, arylboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , 2 M aq.  $\text{K}_2\text{CO}_3$ , DMF, 110 °C, 1 h; j) followed by NMR; k) ArBr,  $\text{Pd}(\text{OAc})_2$ , KOAc, DMA, 150 °C, 25 h (up to 100 h for **5k-m**); l) 81% yield; m) 70% yield

We then applied this established reactivity of 2-(pyridin-4-yl)-DPPs (Scheme 1) to pyridin-2-yl derivatives. Initial screening of the arylation reactions at C3 on a DPP core bearing pyridin-2-yl moiety at C2 started with halogenation at C3 and subsequent cross-coupling. Unfortunately, we observed no reaction whatsoever. We assume that the steric strain between the nitrogen lone electron pair and the bulk bromine atom causes repulsion in **6b**, which leads to the preferred orientation after rotation around the  $\sigma$  bond. This arrangement appears similar to known bidentate ligands such as 2,2'-bipyridyl or 1,10-phenanthroline interacting in the presence of palladium catalyst as shown at Figure 2 (**A – B** resonance). And, in fact, such a highly electron-deficient pyrazole core with a reinforced bond between bromine and the carbon atom is unable

to undergo oxidative addition and, thus, any palladium-catalyzed transformation (Figure 2).

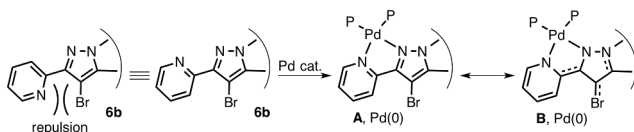
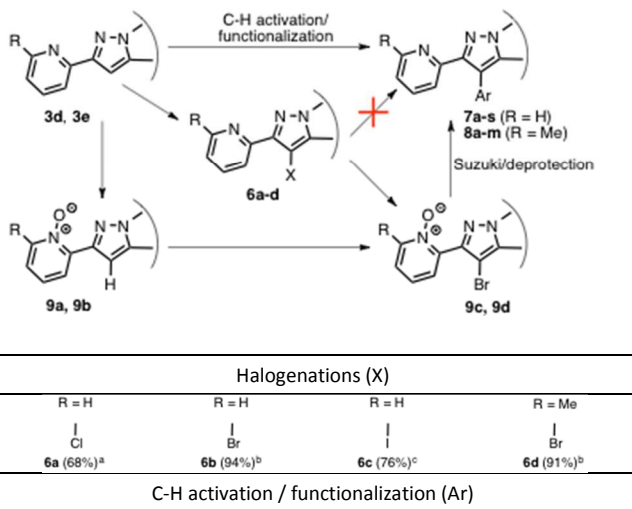


Figure 2. Plausible explanation of the unreactivity of **6b** toward Pd-catalyzed cross-coupling reactions (P = phosphine ligand)

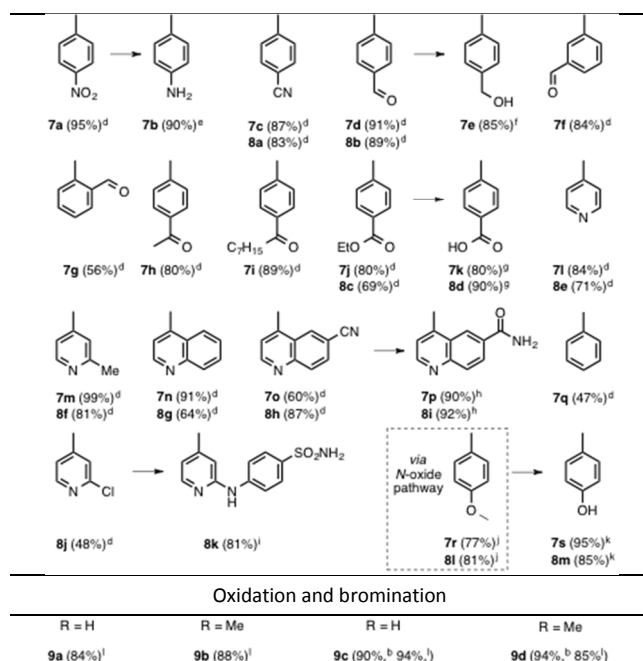
To avoid this complication we protected the pyridine nitrogen atom by transformation to the *N*-oxide (**9c**, **9d**) and, fortunately, such compounds easily afforded the desired Suzuki cross-coupling products in reasonable yields. We chose two examples and obtained products **7d/8b** over two steps (Suzuki and *N*-oxide deprotection) in 64 and 74% yield, respectively, and products **7l/8e** in 53 and 55% yield, respectively (not shown). This simple procedure might be applicable to a much more complex systems and, to our knowledge, has never been applied previously. In fact, there is precedence in the literature<sup>8</sup> where reactions between simple aromatic *N*-oxides and olefins led to *ortho* substituted aromatic *N*-oxides. But the authors clearly demonstrated that without oxidant the reaction did not proceed. In our case Suzuki cross coupling reaction is superior to the *ortho* substitution of pyridin-2-yl *N*-oxide moiety in intermediate **9c** and besides the intermediate **9d** is fully occupied at *ortho* positions. However, in our case, the best candidate for such a transformation is a C-H activation/functionalization sequence where we observed consistently good yields over the reaction course. The only exceptions were the potentially sterically hindered derivative **7g** and reactive

chloropyridyl analog **8j**, which provided lower yields. Likewise, derivative **7q** with simple phenyl substitution presented decreased reactivity in line with the transition from electron-deficient to electron-neutral aromatic substituents. One important highlight worth mentioning is the formation of products **7r/8l** bearing donor substituent. These substrates demonstrate a clear unwillingness to undergo direct C-H activation (we observed only negligible conversions), although *N*-oxide pathway afforded the desired products in high yields (Scheme 2).

Scheme 2. Transformations at C3 on derivatives **3d** and **3e**







a) NCS, anh.  $\text{CHCl}_3$ , rt, 16 h; b) NBS, anh.  $\text{CHCl}_3$ , rt, 0.5 h (**6b**), 0.75 h (**6d**), 1 h (**9c,d**); c) NIS, anh. MeCN, rt, 5.5 h; d) **3d** or **3e**, aryl halide,  $\text{Pd}(\text{OAc})_2$ , KOAc, DMA, 150 °C, 20 – 100 h; e) **7a**, Pd/C,  $\text{H}_2$ , anh. MeOH, rt, 4 h; f) **7d**,  $\text{NaBH}_4$ , anh. MeOH, rt, 0.5 h; g) **7j** or **8c**, 1M NaOH, EtOH/THF, rt, 16 h or 18 h; h) **7o** or **8h**,  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{H}_2\text{O}_2/\text{H}_2\text{O}$ , DMSO, rt, 3–4 h; i) **8j**, sulfanilamide,  $\text{Cs}_2\text{CO}_3$ ,  $\text{Pd}(\text{OAc})_2$ , Xantphos, anh. DMF, 150 °C, 1 h; j) **9c** or **9d**, arylboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , JohnPhos, 2 M aq.  $\text{K}_2\text{CO}_3$ , DMF, 110 °C, 16–25 h, then  $\text{HCOONH}_4$ , Pd/C, anh. MeOH, reflux, 1–2 h; k) 1 M  $\text{BBr}_3$ , anh. DCM, -78 °C to rt, 20 h; l) MCPBA, anh. DCM, 0 °C to rt, 20 h

Optimization of reaction conditions is shown in the SI. Among others, we tried to avoid the use of high boiling solvents, however the best one was DMA followed by DMF. We also tested several strong non-nucleophilic bases including phosphazene P1, Verkade's proazaphosphatane and DBU but without success. Carbonates and phosphates did not work either but KOAc turned out to be the best choice. It worked with a range of palladium catalysts but the combination of palladium acetate/potassium acetate was

revealed to be superior. We attempted the C-H activation in the presence of ligand first but we later determined that the reaction proceeded smoothly even without it. With this knowledge in hand, we were able to propose a reaction mechanism (Figure 3). We assume that in the first step the catalyst coordinates to pyridyl moiety and interacts with a single C-H bond (**P**). Then upon acetic acid departure intermediate **Q** is formed which is in equilibrium with nonreactive palladacycle **R**. Molecule **Q** then undergoes oxidative addition with the respective aryl halide and such a reactive palladium(IV) complex **S** rapidly decomposes and releases desired products **7** after reductive elimination. Finally, the catalytic cycle would end with regeneration of catalyst.

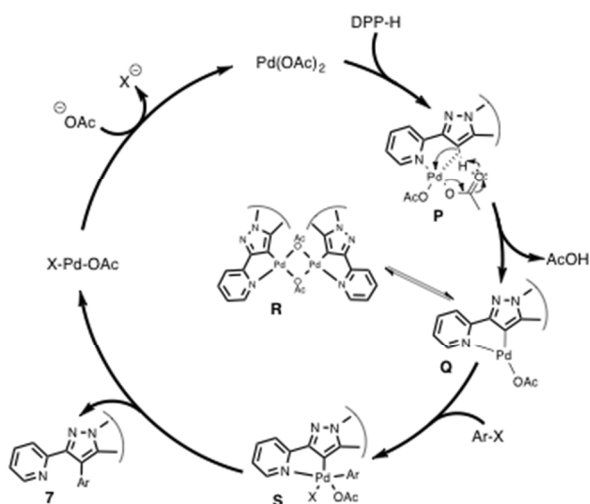


Figure 3. Proposed general catalytic cycle for C-H activation

Due to the known interaction of 2,3-disubstituted DPP in the TGF- $\beta$  signalling pathway,<sup>5d,6g-i</sup> all the compounds were tested in a kinase assay using purified human

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2  
3 ALK5 kinase domain (SI). The assay revealed that the compounds are specific for ALK5  
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5 (over ABL and CDK2) and the structure-activity relationships of novel DPPs are similar to  
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7 those of related known ALK5 inhibitors.<sup>5d,6g-i</sup> Briefly, also our new active compounds  
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9 bear either a pyridin-2-yl (**7l**, **7s**) or 6-methylpyridin-2-yl (**8e-g**, **8i**, **8k**, **8m**) ring at  
10  
11 position C2. Position C3 should be occupied by pyridin-4-yl (**7l**, **8e**), 4-hydroxyphenyl (**7s**,  
12  
13 **8m**) or quinolin-4-yl (**8g**, **8i**) moieties. Further derivatization of the pyridin-4-yl ring at  
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15 position C3 led to the formation of sulfanilamide **8k**, one of the most potent inhibitor  
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17 within this series (Figure 4). Data for the less potent products are summarized in the SI.  
18  
19 Another important finding from our biochemical study was that position C5 of DPP  
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21 tolerates two methyl groups, indicating that the corresponding part of the ALK5's  
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23 binding pocket may be flexible enough to accommodate substitution at this position.  
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25 This has been demonstrated with a 5,5-dimethyl homologue of galunisertib (compound  
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27 **8i**) that also showed activity towards ALK5 (IC<sub>50</sub> value of 0.6 μM). This position of the  
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29 DPP scaffolding has not been previously explored and therefore we chose to prepare  
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31 novel derivatives and study the impact of this modification on biochemical activity.  
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33 Interestingly, quinolyn-4-yl derivatives (**7n-p**, **8g-i**) inhibited also tyrosine kinase ABL,  
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35 suggesting that bulkier C3 substitution may significantly alter the compounds' selectivity  
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37 (see SI). These findings proved that our short synthesis employing non-symmetrical  
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39 homoallenyl azines is a very efficient way to prepare the aforementioned biologically  
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41 active compounds. In addition, apparent broader kinase selectivity of some new  
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43 derivatives may stimulate further studies leading possibly to novel kinase inhibitors.  
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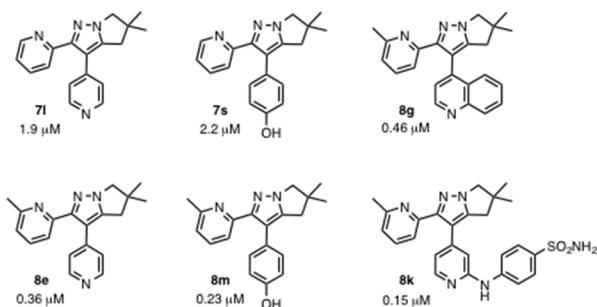


Figure 4. Examples of prepared compounds displaying ALK5 inhibition. Numbers indicate  $IC_{50}$  values.

## Conclusions

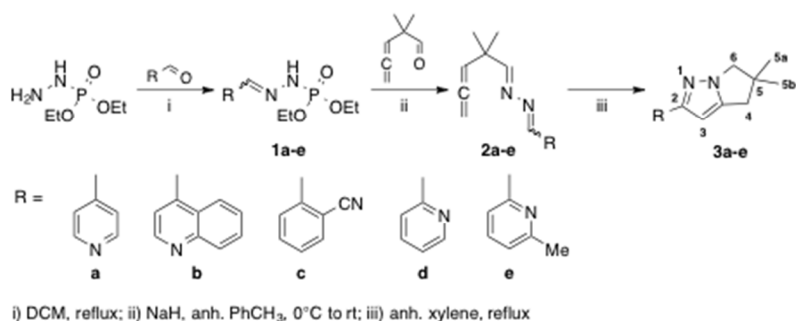
In summary, we describe a straightforward synthesis of novel 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazoles leading to a small library of 57 final products. In the final stage of the synthesis, we exploit Heck, Sonogashira and Suzuki cross-coupling reactions as well as C-H activation and direct arylation methods. We propose a general catalytic cycle to rationalize the C-H activation reaction. Also, we introduce useful protection of pyridin-2-yl nitrogen atom as the *N*-oxide, which facilitated the synthesis of otherwise inaccessible products. Moreover, all synthesized DPP derivatives exhibited reasonable potency and selectivity towards ALK5 kinase and may serve as a starting point for further optimization as kinase inhibitors with possible pharmacological applications.

## Experimental Section

**General Information.** Unless otherwise noted, all reagents were purchased from commercial suppliers and used as received. All reactions were carried out under a dry argon atmosphere. Toluene and xylene were distilled from sodium turnings and stored

over active 3 Å molecular sieves. Melting points were determined in open capillaries. NMR spectra were recorded at 400 MHz ( $^1\text{H}$ ) and 100 MHz ( $^{13}\text{C}$ ) with  $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ ,  $(\text{CD}_3)_2\text{SO}$  or  $\text{CD}_3\text{CN}$  as solvents. Data are presented as follows: chemical shift (in ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constant (J/Hz) and integration. Internal standards (in ppm) for  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were  $\delta$  7.26 and 77.23 for  $\text{CDCl}_3$ ,  $\delta$  3.31 and 49.00 for  $\text{CD}_3\text{OD}$ ,  $\delta$  2.50 and 39.52 for  $(\text{CD}_3)_2\text{SO}$  and  $\delta$  1.94 and 1.32 for  $\text{CD}_3\text{CN}$ . Particular signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were assigned using 2D NMR experiments (HSQC, HMBC). IR spectra of neat compounds or KBr tablets were measured on an FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the positive ESI mode on a LTQ Orbitrap XL, for some azines CI or EI ionization were used. Elemental analyses were performed with a CHN apparatus. Some compounds were purified by preparative HPLC. The analysis was performed using a gradient of 2% B to 70% B over 60 min on a C18, 250  $\times$  20 mm column at a flow rate 10 ml/min, where A: 0.1% TFA/water and B: acetonitrile (210 nm). Column chromatography was performed on Silica gel 60 and thin-layer chromatography (TLC) on Silica gel 60  $\text{F}_{254}$  foils. The diffraction data were collected using diffraction system equipped with rotating anode X-ray source ( $\lambda = 0.71075$  Å), partial  $\chi$  axis goniometer, CCD detector and a cooling device. Structure solution and refinement was performed using SHELX software.<sup>9,10</sup>

#### General Scheme for DPPs 3 preparation and numbering used for NMR characterization



**General Procedure for the Preparation of Protected Hydrazones 1a-e.**<sup>11</sup> To a solution of diethyl hydrazinylphosphonate (7.85 g, 46.7 mmol) in DCM (75 mL) a solution of appropriate aldehyde (46.7 mmol) in DCM (40 mL) in few portions was added (exothermic reaction). The reaction mixture was refluxed using Dean-Stark condenser until the consumption of starting material (1.5 h) and purified.

**Diethyl *N'*-pyridin-4-ylmethylenephosphorohydrazidate (1a).** Column chromatography (MeOH/DCM 1:20) afforded 12.0 g, >99% of colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 9.10 (d, <sup>2</sup>J<sub>P,H</sub> = 29.3, 1H, NH), 8.61 (d, <sup>3</sup>J = 5.9, 2H, 2×CH), 7.83 (s, 1H, CH), 7.48 (d, <sup>3</sup>J = 5.9, 2H, 2×CH), 4.12–4.31 (m, 4H, CH<sub>2</sub>CH<sub>3</sub>), 1.38 (t, <sup>3</sup>J = 7.1, 6H, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 150.2 (2×CH), 142.3 (C), 142.2 (d, <sup>3</sup>J<sub>P,C</sub> = 19.6, CH), 120.8 (2×CH), 63.9 (d, <sup>2</sup>J<sub>P,C</sub> = 5.8, CH<sub>2</sub>CH<sub>3</sub>), 16.3 (d, <sup>3</sup>J<sub>P,C</sub> = 6.8, CH<sub>2</sub>CH<sub>3</sub>). FTIR (neat): 3422, 3129, 2983, 2931, 2910, 2818, 1595, 1548, 1477, 1445, 1408, 1394, 1369, 1234, 1164, 1101, 1018. HRMS (ESI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>10</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>P: 258.1002. Found: 258.1002.

**Diethyl *N'*-quinolin-4-ylmethylenephosphorohydrazidate (1b).** Column chromatography (MeOH/EtOAc 1:8) afforded 13.9 g, 97% of light yellow solid; mp 112.7–113.8 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 9.37 (d, <sup>2</sup>J<sub>P,H</sub> = 29.2, 1H, NH), 8.93 (d, <sup>3</sup>J = 4.5, 1H, CH), 8.54–8.60 (m, 1H, CH), 8.54 (s, 1H, CH), 8.12–8.18 (m, 1H, CH), 7.70–7.78

(m, 1H, CH), 7.68 (d,  $^3J = 4.5$ , 1H, CH), 7.55–7.64 (m, 1H, CH), 4.19–4.39 (m, 4H,  $\text{CH}_2\text{CH}_3$ ), 1.42 (t,  $^3J = 7.0$ , 6H,  $\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  150.2 (CH), 149.1 (C), 141.7 (d,  $^3J_{\text{P,C}} = 20.0$ , CH), 138.1 (C), 130.4 (CH), 129.5 (CH), 127.3 (CH), 125.4 (C), 124.2 (CH), 119.2 (CH), 63.9 (d,  $^2J_{\text{P,C}} = 5.8$ ,  $\text{CH}_2\text{CH}_3$ ), 16.4 (d,  $^3J_{\text{P,C}} = 6.8$ ,  $\text{CH}_2\text{CH}_3$ ). FTIR (neat): 3130, 2959, 2908, 2865, 1607, 1569, 1513, 1391, 1235, 1204, 1171, 1113, 1023. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_3\text{P}$ : 308.1159. Found: 308.1159.

**Diethyl *N'*-(2-cyanophenyl-1-yl)methylenephosphorohydrazidate (1c).** Column chromatography (EtOAc) afforded 12.5 g, 95% of yellowish solid; mp 117.8–119.0 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.50 (d,  $^2J_{\text{P,H}} = 28.9$ , 1H, NH), 8.18 (s, 1H, CH), 7.99 (d,  $^3J = 8.0$ , 1H, CH), 7.64 (d,  $^3J = 7.6$ , 1H, CH), 7.57 (t,  $^3J = 7.7$ , 1H, CH), 7.40 (t,  $^3J = 7.6$ , 1H, CH), 4.13–4.30 (m, 4H,  $\text{CH}_2\text{CH}_3$ ), 1.37 (t,  $^3J = 7.0$ , 6H,  $\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  140.5 (d,  $^3J_{\text{P,C}} = 19.6$ , CH), 137.4 (C), 133.1 (CH), 132.9 (CH), 129.3 (CH), 126.3 (CH), 117.3 (CH), 110.9 (CN), 63.8 (d,  $^2J_{\text{P,C}} = 5.6$ ,  $\text{CH}_2\text{CH}_3$ ), 16.3 (d,  $^3J_{\text{P,C}} = 6.9$ ,  $\text{CH}_2\text{CH}_3$ ). FTIR (neat): 3323, 3139, 3002, 2941, 2932, 2910, 2227, 1608, 1590, 1565, 1470, 1442, 1394, 1371, 1296, 1243, 1165, 1119, 1028, 982. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_3\text{P}$ : 282.1002. Found: 282.1003.

**Diethyl *N'*-pyridin-2-ylmethylenephosphorohydrazidate (1d).** Column chromatography (MeOH/DCM 1:20) afforded 12.0 g, >99% of colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.71 (d,  $^2J_{\text{P,H}} = 28.8$ , 1H, NH), 8.54–8.60 (m, 1H, CH), 8.01 (s, 1H, CH), 7.87–7.95 (m, 1H, CH), 7.62–7.71 (m, 1H, CH), 7.17–7.25 (m, 1H, CH), 4.10–4.32 (m, 4H,  $\text{CH}_2\text{CH}_3$ ), 1.37 (t,  $^3J = 7.1$ , 6H,  $\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  153.9 (C), 149.3 (CH), 145.6 (d,  $^3J_{\text{P,C}} = 19.0$ , CH), 136.4 (CH), 123.5 (CH), 120.1 (CH), 63.5 (d,  $^2J_{\text{P,C}} = 5.5$ ,  $\text{CH}_2\text{CH}_3$ ), 16.3 (d,

$^3J_{P,C} = 6.8$ ,  $\text{CH}_2\text{CH}_3$ ). FTIR (neat): 3469, 3056, 2983, 2929, 2909, 2855, 1594, 1556, 1474, 1445, 1411, 1392, 1293, 1244, 1164, 1100, 1018. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd. for  $\text{C}_{10}\text{H}_{16}\text{N}_3\text{O}_3\text{NaP}$ : 280.0822. Found: 280.0822.

**Diethyl *N'*-(6-methylpyridin-2-yl)methylenephosphorohydrazidate (1e).** Column chromatography (EtOAc/DCM 1:20) afforded 12.5 g, >99% of colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.09 (d,  $^2J_{P,H} = 28.6$ , 1H, NH), 7.88 (s, 1H, CH), 7.70 (d,  $^3J = 7.8$ , 1H, CH), 7.55 (t,  $^3J = 7.7$ , 1H, CH), 7.06 (d,  $^3J = 7.5$ , 1H, CH), 4.02–4.29 (m, 4H,  $\text{CH}_2\text{CH}_3$ ), 2.52 (s, 3H,  $\text{CH}_3\text{-Ar}$ ), 1.34 (t,  $^3J = 7.0$ , 6H,  $\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  158.0 (C), 153.1 (C), 145.8 (d,  $^3J_{P,C} = 18.6$ , CH), 136.6 (CH), 123.2 (CH), 117.2 (CH), 63.6 (d,  $^2J_{P,C} = 5.5$ ,  $\text{CH}_2\text{CH}_3$ ), 24.4 ( $\text{CH}_3\text{-Ar}$ ), 16.3 (d,  $^3J_{P,C} = 6.9$ ,  $\text{CH}_2\text{CH}_3$ ). FTIR (neat): 3325, 3141, 3067, 2995, 2942, 2932, 2910, 2870, 1603, 1589, 1573, 1479, 1452, 1443, 1395, 1377, 1370, 1320, 1292, 1243, 1156, 1106, 980. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{11}\text{H}_{19}\text{N}_3\text{O}_3\text{P}$ : 272.1159. Found: 272.1159.

#### General Procedure for the Preparation of Nonsymmetrical Homoallenyl Azines 2a-e.

To an anhydrous toluene (50 mL) was added NaH (636 mg, 26.5 mmol, 1.5 equiv.) and the mixture was cooled down to 0 °C. To this suspension a solution of 2,2-dimethylpenta-3,4-dienal<sup>12</sup> (1.96 g, 17.7 mmol) and protected hydrazone **1a-e** (19.4 mmol, 1.1 equiv.) in anhydrous toluene (20 mL) was added dropwise over a period of 15 min. The temperature was kept within 0–5 °C range. The reaction mixture was left to heat up to rt. When the starting material disappeared on TLC (1-2 h), the mixture was filtered and the solid residue was washed with  $\text{Et}_2\text{O}$  and DCM (3×10 mL each). Solvent was evaporated and products were purified.



**4-(((2,2-Dimethylpenta-3,4-dienylidene)hydrazono)methyl)pyridine (2a).** Column chromatography (EtOAc) afforded 3.13 g, 83% of light yellow liquid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.70 (d,  $^3J = 4.7$ , 2H, 2 $\times$ CH), 8.38 (s, 1H, CH), 7.85 (s, 1H, CH), 7.61 (d,  $^3J = 4.7$ , 2H, 2 $\times$ CH), 5.28 (t,  $^4J = 6.6$ , 1H,  $\text{HC}=\text{C}=\text{CH}_2$ ), 4.86 (d,  $^4J = 6.6$ , 2H,  $=\text{CH}_2$ ), 1.32 (s, 6H,  $\text{H}_3\text{C}-\text{C}-\text{CH}_3$ ).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  207.2 ( $=\text{C}=\text{N}$ ), 171.1 ( $\text{HC}=\text{N}$ ), 158.3 ( $\text{HC}=\text{N}$ ), 150.6 (2 $\times$ CH), 141.2 (C), 122.0 (2 $\times$ CH), 97.2 ( $=\text{CH}_2$ ), 78.0 ( $\text{HC}=\text{C}$ ), 38.4 ( $\text{H}_3\text{C}-\text{C}-\text{CH}_3$ ), 25.6 ( $\text{H}_3\text{C}-\text{C}-\text{CH}_3$ ). FTIR (neat): 2969, 2930, 2886, 2868, 1954, 1646, 1594, 1552, 1463, 1444, 1408, 1384, 1363, 1310, 1233, 1195, 1147, 990. HRMS (EI)  $m/z$ :  $[\text{M}]^+$  Calcd. for  $\text{C}_{13}\text{H}_{15}\text{N}_3$ : 213.1266. Found: 213.1263.

**4-(((2,2-Dimethylpenta-3,4-dienylidene)hydrazono)methyl)quinoline (2b).** Column chromatography (EtOAc) afforded 3.64 g, 78% of yellow liquid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  9.07 (s, 1H, CH), 8.99 (d,  $^3J = 4.5$ , 1H, CH), 8.66 (d,  $^3J = 8.4$ , 1H, CH), 8.18 (d,  $^3J = 8.4$ , 1H, CH), 7.98 (s, 1H, CH), 7.80 (d,  $^3J = 4.5$ , 1H, CH), 7.72–7.79 (m, 1H, CH), 7.59–7.66 (m, 1H, CH), 5.33 (t,  $^4J = 6.7$ , 1H,  $\text{HC}=\text{C}=\text{CH}_2$ ), 4.88 (d,  $^4J = 6.7$ , 2H,  $=\text{CH}_2$ ), 1.36 (s, 6H,  $\text{H}_3\text{C}-\text{C}-\text{CH}_3$ ).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  207.3 ( $=\text{C}=\text{N}$ ), 171.6 ( $\text{HC}=\text{N}$ ), 158.1 ( $\text{HC}=\text{N}$ ), 150.3 (CH), 149.2 (C), 137.5 (C), 130.5 (CH), 129.8 (CH), 127.8 (CH), 125.9 (C), 124.4 (CH), 120.8 (CH), 97.3 ( $=\text{CH}_2$ ), 78.1 ( $\text{HC}=\text{C}$ ), 38.5 ( $\text{H}_3\text{C}-\text{C}-\text{CH}_3$ ), 25.7 ( $\text{H}_3\text{C}-\text{C}-\text{CH}_3$ ). FTIR (neat): 3058, 3034, 2968, 2929, 2885, 2867, 1954, 1704, 1646, 1610, 1581, 1562, 1506, 1462, 1424, 1385, 1361, 1323, 1302, 1250, 1211, 1161, 1137, 1088. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{17}\text{H}_{18}\text{N}_3$ : 264.1495. Found: 264.1496.

**3-(((2,2-Dimethylpenta-3,4-dien-1-ylidene)hydrazono)methyl)benzonitrile (2c).** Column chromatography (EtOAc/hexane 1:8) afforded 3.23 g, 77% of light yellow liquid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.79 (s, 1H, CH), 8.18 (d, <sup>3</sup>J = 7.9, 1H, CH), 7.87 (s, 1H, CH), 7.74 (d, <sup>3</sup>J = 7.6, 1H, CH), 7.66 (t, <sup>3</sup>J = 7.4, 1H, CH), 7.54 (t, <sup>3</sup>J = 7.6, 1H, CH), 5.26 (t, <sup>4</sup>J = 6.7, 1H, HC=C=CH<sub>2</sub>), 4.84 (d, <sup>4</sup>J = 6.7, 2H, =CH<sub>2</sub>), 1.27 (s, 6H, H<sub>3</sub>C-C-CH<sub>3</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 207.1 (=C=), 168.7 (HC=N), 156.3 (HC=N), 136.6 (C), 133.4 (CH), 133.0 (CH), 131.0 (CH), 127.5 (CH), 117.0 (C), 113.0 (CN), 97.3 (=CH<sub>2</sub>), 77.8 (HC=C), 38.1 (H<sub>3</sub>C-C-CH<sub>3</sub>), 25.6 (H<sub>3</sub>C-C-CH<sub>3</sub>). FTIR (neat): 3059, 2969, 2929, 2887, 2868, 2224, 1955, 1700, 1647, 1627, 1593, 1465, 1384, 1363, 1309, 1288, 1222, 1194, 1147, 1090, 1018, 991. HRMS (CI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>15</sub>H<sub>16</sub>N<sub>3</sub>: 238.1344. Found: 238.1346.

**2-(((2,2-Dimethylpenta-3,4-dienylidene)hydrazono)methyl)pyridine (2d).** Column chromatography (EtOAc) afforded 3.47 g, 92% of light yellow liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.65–8.69 (m, 1H, CH), 8.47 (s, 1H, CH), 7.96–8.01 (m, 1H, CH), 7.85 (s, 1H, CH), 7.69–7.77 (m, 1H, CH), 7.27–7.33 (m, 1H, CH), 5.30 (t, <sup>4</sup>J = 6.7, 1H, HC=C=CH<sub>2</sub>), 4.85 (d, <sup>4</sup>J = 6.7, 2H, =CH<sub>2</sub>), 1.32 (s, 6H, H<sub>3</sub>C-C-CH<sub>3</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 207.1 (=C=), 170.0 (HC=N), 160.2 (HC=N), 153.1 (C), 149.9 (CH), 136.5 (CH), 124.8 (CH), 122.0 (CH), 97.2 (=CH<sub>2</sub>), 77.8 (HC=C), 38.2 (H<sub>3</sub>C-C-CH<sub>3</sub>), 25.5 (H<sub>3</sub>C-C-CH<sub>3</sub>). FTIR (neat): 3056, 2968, 2929, 2886, 2867, 1954, 1646, 1630, 1586, 1567, 1465, 1436, 1384, 1363, 1309, 1218, 1194, 1148, 1090, 1044, 992. HRMS (EI) *m/z*: [M]<sup>+</sup> Calcd. for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>: 213.1266. Found: 213.1262.

**2-(((2,2-Dimethylpenta-3,4-dienylidene)hydrazono)methyl)-6-methylpyridine (2e).** Column chromatography (EtOAc/hexane 1:4) afforded 3.50 g, 87% of light yellow liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.38 (s, 1H, CH), 7.78 (s, 1H, CH), 7.72 (d, <sup>3</sup>J = 7.7, 1H, CH), 7.59 (t, <sup>3</sup>J = 7.7, 1H, CH), 7.14 (d, <sup>3</sup>J = 7.7, 1H, CH), 5.25 (t, <sup>4</sup>J = 6.7, 1H, HC=C=CH<sub>2</sub>), 4.80

(d,  $^4J = 6.7$ , 2H, =CH<sub>2</sub>), 2.56 (s, 3H, CH<sub>3</sub>-Ar), 1.27 (s, 6H, H<sub>3</sub>C-C-CH<sub>3</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 207.1 (=C=), 169.6 (HC=N), 160.2 (HC=N), 158.7 (C), 152.4 (C), 136.7 (CH), 124.6 (CH), 119.4 (CH), 97.2 (=CH<sub>2</sub>), 77.8 (HC=C), 38.2 (H<sub>3</sub>C-C-CH<sub>3</sub>), 25.5 (H<sub>3</sub>C-C-CH<sub>3</sub>), 24.5 (CH<sub>3</sub>-Ar). FTIR (neat): 3058, 2966, 2926, 2855, 1955, 1699, 1647, 1630, 1587, 1568, 1456, 1384, 1372, 1363, 1301, 1249, 1237, 1221, 1145, 1083, 1039, 986, 958. HRMS (CI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>14</sub>H<sub>18</sub>N<sub>3</sub>: 228.1501. Found: 228.1502.

**General Procedure for the Preparation of Starting DPPs 3a-e.** 3.00 g of nonsymmetrical homoallenyl azine **2a-e** was dissolved in anhydrous xylene (25 mL, mixture of isomers) and refluxed under an argon atmosphere (8 h for **3a,d**; 9 h for **3b**; 4 h for **3c**; 7 h for **3d**). Solvent was evaporated and the crude product was purified by column chromatography (EtOAc for **3a,b,d** and EtOAc/hexane 1:3 for **3c,e**).

**5,5-Dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (3a).** Yield 2.76 g, 92% of yellow-orange solid; mp 109.5–109.8 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 8.59 (dd,  $^3J = 4.6$ , 1.6, 2H, 2×CH), 7.64 (dd,  $^3J = 4.6$ , 1.6, 2H, 2×CH), 6.36 (s, 1H, H3), 3.94 (s, 2H, H6), 2.73 (s, 2H, H4), 1.32 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ<sub>C</sub> 152.9 (C), 150.4 (C), 146.8 (2×CH), 141.7 (C), 119.8 (2×CH), 97.7 (C3), 61.4 (C6), 43.3 (C5), 39.0 (C4), 28.3 (C5a,b). FTIR (neat): 3034, 2965, 2932, 2873, 1601, 1557, 1536, 1514, 1467, 1435, 1419, 1366, 1315, 1219, 1202, 1172, 988. Anal. Calcd. for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>: C, 73.21; H, 7.09; N, 19.70. Found: C, 72.89; H, 7.03; N, 19.90.

**4-(5,5-Dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)quinoline (3b).** Yield 2.76 g, 92% of yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 8.91 (d,  $^3J = 4.5$ , 1H, CH), 8.74 (d,  $^3J = 8.5$ , 1H, CH), 8.14 (d,  $^3J = 8.4$ , 1H, CH), 7.71 (t,  $^3J = 7.6$ , 1H, CH), 7.58 (d,  $^3J = 4.4$ , 1H, CH), 7.54 (t,  $^3J =$

7.2, 1H, CH), 6.37 (s, 1H, H3), 4.01 (s, 2H, H6), 2.78 (s, 2H, H4), 1.35 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  152.8 (C), 150.2 (CH), 149.2 (C), 146.1 (C), 140.4 (C), 129.9 (CH), 129.3 (CH), 126.8 (CH), 126.7 (CH), 126.2 (C), 120.5 (CH), 100.9 (C3), 61.5 (C6), 43.3 (C5), 39.0 (C4), 28.4 (C5a,b). FTIR (neat): 3042, 2957, 2870, 1583, 1565, 1541, 1511, 1467, 1439, 1419, 1381, 1370, 1353, 1318, 1284, 1268, 1215, 1177, 1024. HRMS (ESI)  $m/z$ : [ $\text{M} + \text{H}$ ] $^+$  Calcd. for  $\text{C}_{17}\text{H}_{17}\text{N}_3$ : 264.1495. Found: 264.1492.

**2-(5,5-Dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)benzonitrile (3c).** Yield 2.46 g, 82% of light yellow solid; mp 83.2–84.3 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.93–7.97 (m, 1H, CH), 7.66–7.70 (m, 1H, CH), 7.54–7.60 (m, 1H, CH), 7.31–7.36 (m, 1H, CH), 6.68 (s, 1H, H3), 3.94 (s, 2H, H6), 2.74 (s, 2H, H4), 1.31 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  151.8 (C), 146.5 (C), 137.6 (C), 134.0 (CH), 132.8 (CH), 128.3 (CH), 127.4 (CH), 119.5 (C), 109.2 (CN), 99.5 (C3), 61.3 (C6), 43.2 (C5), 38.9 (C4), 28.3 (C5a,b). FTIR (neat): 2965, 2931, 2882, 2873, 2860, 2226, 1600, 1540, 1504, 1486, 1464, 1452, 1441, 1415, 1390, 1372, 1354, 1326, 1301, 1287, 1272, 1252, 1231, 1200, 1174, 1164, 1105, 1069, 1035, 967. HRMS (ESI)  $m/z$ : [ $\text{M} + \text{H}$ ] $^+$  Calcd. for  $\text{C}_{15}\text{H}_{16}\text{N}_3$ : 238.1339. Found: 238.1339.

**5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (3d).** Yield 2.64 g, 88% of light yellow-orange solid; mp 92.4–93.2 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.58–8.62 (m, 1H, CH), 7.87–7.91 (m, 1H, CH), 7.64–7.71 (m, 1H, CH), 7.13–7.18 (m, 1H, CH), 6.60 (s, 1H, H3), 3.94 (s, 2H, H6), 2.74 (s, 2H, H4), 1.32 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  155.8 (C), 153.1 (C), 149.5 (CH), 146.4 (C), 136.5 (CH), 122.2 (CH), 119.8 (CH), 98.2 (C3), 61.3 (C6), 43.3 (C5), 39.0 (C4), 28.3 (C5a,b). FTIR (neat): 3044, 3006, 2960, 2931, 2868, 1587, 1563, 1499, 1473, 1451, 1409, 1387, 1370, 1362, 1316, 1271, 1201, 1143, 1126, 1088,

1060, 1041, 991. Anal. Calcd. for  $C_{13}H_{15}N_3$ : C, 73.21; H, 7.09; N, 19.70. Found: C, 73.09; H, 7.17; N, 19.88.

**5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (3e).**

Yield 2.58 g, 86% of light yellow solid; mp 101.6–102.8 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  7.62 (d,  $^3J$  = 7.8, 1H, CH), 7.56 (t,  $^3J$  = 7.7, 1H, CH), 7.03 (d,  $^3J$  = 7.5, 1H, CH), 6.56 (s, 1H, H3), 3.94 (s, 2H, H6), 2.72 (s, 2H, H4), 2.59 (s, 3H,  $CH_3$ -Ar), 1.30 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  158.1 (C), 155.8 (C), 152.3 (C), 146.1 (C), 136.6 (CH), 121.6 (CH), 116.8 (CH), 98.1 (C3), 61.1 (C6), 43.2 (C5), 38.8 (C4), 28.1 (C5a,b), 24.7 ( $CH_3$ -Ar). FTIR (neat): 2959, 2924, 2876, 2867, 1591, 1573, 1544, 1496, 1453, 1429, 1407, 1386, 1369, 1348, 1322, 1268, 1199, 1171, 1154, 1128, 1091, 1073, 1007, 991. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{14}H_{17}N_3$ : 228.1495. Found: 228.1497.

*Alternative Method:* **3d** (1.00 g, 4.69 mmol) was dissolved in anhydrous  $Et_2O$  (50 mL) and the solution was cooled down to -70 °C under an argon atmosphere. A 1.6 M solution of methyl lithium (7.3 mL, 11.7 mmol, 2.5 equiv.) was added dropwise. The red mixture was stirred for 0.5 h at the same temperature and then heated up to rt and stirred for 1 h. The reaction was quenched with sat.  $NH_4Cl$  (12 mL) and water (10 mL). Water phase was extracted with DCM (2×25 mL), combined organic phases were dried over  $Na_2SO_4$ , filtered and evaporated. The crude product was purified by column chromatography ( $EtOAc/DCM$  1:1) to yield 362 mg (34%) of desired product.

**Pyridin-4-yl, Quinolin-4-yl and 2-Cyanophenyl Substituted Products at C2:**  
**Halogenations.**

**3-Chloro-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (4a).** **3a**

(1.00 g, 4.69 mmol) was dissolved in anhydrous  $\text{CHCl}_3$  (40 mL) and NCS (2.50 g, 18.8 mmol, 4 equiv.) was added in few portions. The reaction mixture was stirred for 18 hours at rt under an argon atmosphere. The mixture was washed with 10% aq.  $\text{Na}_2\text{SO}_4$  (25 mL) and then with water (3×25 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated. Column chromatography (EtOAc) afforded 1.05 g, 91% of light yellow solid; mp 54.2–55.0 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.61 (dd,  $^3J = 4.6, 1.6$ , 2H, 2×CH), 7.84 (dd,  $^3J = 4.6, 1.6$ , 2H, 2×CH), 3.92 (s, 2H, H6), 2.72 (s, 2H, H4), 1.31 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  149.8 (2×CH), 147.4 (C), 144.3 (C), 140.4 (C), 121.0 (2×CH), 103.1 (C3), 62.3 (C6), 43.2 (C5), 38.1 (C4), 28.3 (C5a,b). FTIR (neat): 2959, 2933, 2905, 2870, 2853, 1599, 1558, 1464, 1434, 1416, 1360, 1333, 1262, 1219, 1024, 989. HRMS (ESI)  $m/z$ : [ $\text{M} + \text{H}$ ] $^+$  Calcd. for  $\text{C}_{13}\text{H}_{14}\text{N}_3\text{Cl}$ : 248.0949. Found: 248.0952.

**3-Bromo-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (4b).** **3a**

(1.00 g, 4.69 mmol) was dissolved in anhydrous  $\text{CHCl}_3$  (20 mL) and NBS (0.96 g, 5.39 mmol, 1.15 equiv.) was added in few portions. The reaction mixture was stirred for 1 h at rt under an argon atmosphere. DCM (20 mL) was added and the mixture was washed with 10% aq.  $\text{Na}_2\text{S}_2\text{O}_5$  (10 mL) and water (3×20 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated. Column chromatography (EtOAc/DCM 1:1) afforded 1.28 g, 93% of light yellow-orange solid; mp 73.3–74.0 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.64 (d,  $^3J = 6.0$ , 2H, 2×CH), 7.86 (d,  $^3J = 6.0$ , 2H, 2×CH), 3.98 (s, 2H, H6), 2.73 (s, 2H, H4), 1.35 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  150.0 (2×CH), 148.9 (C), 146.5 (C), 140.5 (C), 121.2 (2×CH), 86.6 (C3), 62.4 (C6), 42.9 (C5), 38.4 (C4), 28.3 (C5a,b). FTIR (neat): 3035, 2968,

2951, 2932, 2902, 2877, 2848, 1597, 1556, 1539, 1465, 1449, 1428, 1414, 1390, 1371, 1354, 1322, 1255, 1219, 1173, 1008, 990. Anal. Calcd. for  $C_{13}H_{14}N_3Br$ : C, 53.44; H, 4.83; N, 14.38. Found: C, 53.77; H, 4.85; N, 14.20.

**3-Iodo-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (4c). 3a**

(1.00 g, 4.69 mmol) was dissolved in a mixture of anhydrous MeCN (25 mL) and anhydrous  $CHCl_3$  (15 mL). NIS (3.16 g, 14.1 mmol, 3 equiv.) was added in few portions. The reaction mixture was stirred for 0.5 h at rt and then refluxed for 17 h under an argon atmosphere. Solvents were evaporated and the residue was dissolved in DCM (30 mL), washed with 10% aq.  $Na_2S_2O_5$  (30 mL) and water (3×30 mL). Combined water phases were extracted with DCM (10 mL). Organic layers were dried over  $Na_2SO_4$  and solvent was evaporated. Column chromatography (EtOAc) afforded 1.29 g, 81% of an off-white solid; mp 119.8–120.0 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.65 (dd,  $^3J = 4.6, 1.6$ , 2H, 2×CH), 7.84 (dd,  $^3J = 4.6, 1.6$ , 2H, 2×CH), 4.02 (s, 2H, H6), 2.71 (s, 2H, H4), 1.34 (s, 6H, H5a,b).  $^{13}C$  { $^1H$ } NMR ( $CDCl_3$ ):  $\delta_C$  152.0 (C), 150.9 (C), 150.1 (2×CH), 141.1 (C), 121.7 (2×CH), 62.6 (C6), 50.2 (C3), 42.6 (C5), 39.2 (C4), 28.4 (C5a,b). FTIR (neat): 3080, 3030, 2961, 2939, 2906, 2871, 2851, 1601, 1550, 1524, 1483, 1438, 1424, 1412, 1373, 1352, 1320, 1263, 1229, 1213, 1175, 1156, 1106, 1064, 1002, 992. Anal. Calcd. for  $C_{13}H_{14}N_3I$ : C, 46.03; H, 4.16; N, 12.39. Found: C, 46.18; H, 4.20; N, 12.26.

**4-(3-Bromo-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)quinoline (4d).**

Follow the same procedure as for product **4b**, reaction time was 1.5 h. **3b** (1.0 g, 3.80 mmol) and *N*-bromosuccinimide (811 mg, 4.56 mmol, 1.2 equiv.) afforded after column chromatography (EtOAc/DCM 1:1) 1.16 g, 89% of light yellow-orange solid; mp 115.4–

116.7 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.98 (d,  $^3J = 4.4$ , 1H, CH), 8.23 (d,  $^3J = 8.3$ , 1H, CH), 8.17 (d,  $^3J = 8.4$ , 1H, CH), 7.72 (t,  $^3J = 7.2$ , 1H, CH), 7.57 (d,  $^3J = 4.4$ , 1H, CH), 7.54 (t,  $^3J = 7.3$ , 1H, CH), 4.04 (s, 2H, H6), 2.78 (s, 2H, H4), 1.37 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  150.1 (C), 149.8 (CH), 148.9 (C), 145.8 (C), 138.6 (C), 129.8 (CH), 129.5 (CH), 126.9 (CH), 126.8 (CH), 126.7 (C), 122.3 (CH), 88.4 (C3), 62.6 (C6), 43.1 (C5), 38.6 (C4), 28.4 (C5a,b). FTIR (neat): 2958, 2928, 2868, 1586, 1565, 1544, 1514, 1471, 1450, 1370, 1349, 1311, 1286, 1266, 1175, 1139, 1119, 1046. Anal. Calcd. For  $\text{C}_{17}\text{H}_{16}\text{N}_3\text{Br}$ : C, 59.66; H, 4.71; N, 12.28. Found: C, 59.57; H, 4.75; N, 12.09.

**2-(3-Bromo-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)benzonitrile (4e).**

Follow the same procedure as for product **4b**, reaction time was 1.5 h. **3c** (1.00 g, 4.21 mmol) and *N*-bromosuccinimide (1.13 g, 6.32 mmol, 1.5 equiv.) afforded after column chromatography (EtOAc/hexane 1:4) 1.27 g, 95% of light yellow solid; mp 118.1–119.6 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.75–7.79 (m, 1H, CH), 7.69–7.72 (m, 1H, CH), 7.61–7.66 (m, 1H, CH), 7.44–7.49 (m, 1H, CH), 4.01 (s, 2H, H6), 2.75 (s, 2H, H4), 1.36 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  149.9 (C), 145.7 (C), 135.9 (C), 133.8 (CH), 132.3 (CH), 130.6 (CH), 128.5 (CH), 118.5 (C), 112.4 (CN), 87.4 (C3), 62.4 (C6), 42.9 (C5), 38.5 (C4), 28.4 (C5a,b). FTIR (neat): 3072, 2986, 2976, 2961, 2927, 2904, 2881, 2871, 2226, 1597, 1541, 1486, 1463, 1455, 1449, 1433, 1417, 1400, 1390, 1373, 1349, 1339, 1316, 1300, 1288, 1277, 1266, 1257, 1176, 1162, 1111, 1088, 1040, 1028, 1004, 984. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{Br}$ : 316.0444. Found: 316.0446.

**Pyridin-4-yl Substituted Products at C2: Heck Cross-Coupling and Related Products. 4b**

(100 mg, 0.342 mmol) and  $\text{Pd}(\text{dba})_2$  (9.8 mg, 5 mol% for **5a,b** and 20 mg, 10 mol% for **5c**)



were dissolved in anhydrous DMF (2 mL). Et<sub>3</sub>N (95  $\mu$ L, 2 equiv.), P(*t*-Bu)<sub>3</sub> (8  $\mu$ L, 10 mol% for **5a,b** and 13  $\mu$ L, 15 mol% for **5c**) and relevant alkene - 4-methoxystyrene (91  $\mu$ L, 2 equiv. for **5a**), 4-methylstyrene (68  $\mu$ L, 1.5 equiv. for **5b**) or methyl acrylate (155  $\mu$ L, 5 equiv. for **5c**) were added. The mixture was stirred at 100 °C under an argon atmosphere for 2 h (**5a**), 8 h (**5b**) or 4 h (**5c**). DMF was evaporated and the crude product was purified by column chromatography (EtOAc). Both *cis* and *trans* isomers formed in **5a** and **5b** were separated during the purification.

**3-(4-Methoxystyryl)-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-**

**b]pyrazole (**5a**).** Yield 107 mg, 90%; *cis/trans* 35:65, *cis* - yellow oil, *trans* - a colorless solid; mp 121.0–121.9 °C. *cis* isomer: <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta_{\text{H}}$  8.43 (d, <sup>3</sup>*J* = 6.1, 2H, 2 $\times$ CH), 7.52 (d, <sup>3</sup>*J* = 6.1, 2H, 2 $\times$ CH), 7.29 (d, <sup>3</sup>*J* = 8.8, 2H, 2 $\times$ CH), 6.78 (d, <sup>3</sup>*J* = 8.8, 2H, 2 $\times$ CH), 5.56 (d, <sup>3</sup>*J* = 1.2, 1H, CH), 5.11 (d, <sup>3</sup>*J* = 1.2, 1H, CH), 3.97 (s, 2H, H<sub>6</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 2.53 (s, 2H, H<sub>4</sub>), 1.30 (s, 6H, H<sub>5a,b</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>):  $\delta_{\text{C}}$  159.7 (C), 150.5 (C), 149.8 (2 $\times$ CH), 146.4 (C), 141.8 (C), 140.1 (CH), 132.8 (C), 128.1 (2 $\times$ CH), 121.9 (2 $\times$ CH), 115.0 (C<sub>3</sub>), 114.2 (CH), 113.9 (2 $\times$ CH), 61.6 (C<sub>6</sub>), 55.4 (OCH<sub>3</sub>), 43.2 (C<sub>5</sub>), 38.7 (C<sub>4</sub>), 28.3 (C<sub>5a,b</sub>). *trans* isomer: <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta_{\text{H}}$  8.65 (d, <sup>3</sup>*J* = 5.7, 2H, 2 $\times$ CH), 7.59 (d, <sup>3</sup>*J* = 5.7, 2H, 2 $\times$ CH), 7.35 (d, <sup>3</sup>*J* = 8.6, 2H, 2 $\times$ CH), 6.94 (d, <sup>3</sup>*J* = 16.3, 1H, CH), 6.87 (d, <sup>3</sup>*J* = 8.6, 2H, 2 $\times$ CH), 6.62 (d, <sup>3</sup>*J* = 16.3, 1H, CH), 3.94 (s, 2H, H<sub>6</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 2.91 (s, 2H, H<sub>4</sub>), 1.36 (s, 6H, H<sub>5a,b</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>):  $\delta_{\text{C}}$  159.1 (C), 150.7 (C), 150.0 (2 $\times$ CH), 143.7 (C), 141.8 (C), 130.4 (C), 128.0 (CH), 127.1 (2 $\times$ CH), 122.4 (2 $\times$ CH), 117.2 (CH), 114.2 (2 $\times$ CH), 112.6 (C<sub>3</sub>), 61.2 (C<sub>6</sub>), 55.3 (OCH<sub>3</sub>), 43.2 (C<sub>5</sub>), 39.9 (C<sub>4</sub>), 28.4 (C<sub>5a,b</sub>). FTIR (neat, *cis*): 3034, 2958, 2930, 2872, 2838, 1642, 1600, 1574, 1509, 1462, 1437, 1415, 1389, 1370, 1323, 1305, 1293,

1248, 1173, 1162, 1112, 1065, 1029, 992; *trans*: 3035, 2961, 2930, 2905, 2874, 2836, 1597, 1509, 1487, 1464, 1435, 1417, 1370, 1320, 1305, 1292, 1274, 1250, 1219, 1173, 1116, 1035, 991. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{22}H_{23}N_3O$ : 346.1914. Found: 346.1909.

**5,5-Dimethyl-3-(4-methylstyryl)-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole**

**(5b)**. Yield 106 mg, 94%; *cis/trans* 28:72, *cis* - yellow oil, *trans* - a colorless solid; mp 118.5–118.6 °C. *cis* isomer:  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.42 (d,  $^3J = 6.1$ , 2H, 2 $\times$ CH), 7.52 (d,  $^3J = 6.1$ , 2H, 2 $\times$ CH), 7.26 (d,  $^3J = 8.1$ , 2H, 2 $\times$ CH), 7.06 (d,  $^3J = 8.1$ , 2H, 2 $\times$ CH), 5.62 (d,  $^3J = 1.2$ , 1H, CH), 5.16 (d,  $^3J = 1.2$ , 1H, CH), 3.97 (s, 2H, H6), 2.51 (s, 2H, H4), 2.31 (s, 3H, Ph-CH<sub>3</sub>), 1.30 (s, 6H, H5a,b).  $^{13}C$  { $^1H$ } NMR ( $CDCl_3$ ):  $\delta_C$  150.5 (C), 149.8 (2 $\times$ CH), 146.3 (C), 141.8 (C), 140.6 (CH), 138.0 (C), 137.3 (C), 129.2 (2 $\times$ CH), 126.8 (2 $\times$ CH), 121.9 (2 $\times$ CH), 115.1 (CH), 114.9 (C3), 61.6 (C6), 43.2 (C5), 38.7 (C4), 28.3 (C5a,b), 21.3 (Ph-CH<sub>3</sub>). *trans* isomer:  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.65 (d,  $^3J = 5.8$ , 2H, 2 $\times$ CH), 7.58 (d,  $^3J = 5.8$ , 2H, 2 $\times$ CH), 7.31 (d,  $^3J = 8.0$ , 2H, 2 $\times$ CH), 7.13 (d,  $^3J = 8.0$ , 2H, 2 $\times$ CH), 7.03 (d,  $^3J = 16.3$ , 1H, CH), 6.64 (d,  $^3J = 16.3$ , 1H, CH), 3.94 (s, 2H, H6), 2.91 (s, 2H, H4), 2.33 (s, 3H, Ph-CH<sub>3</sub>), 1.36 (s, 6H, H5a,b).  $^{13}C$  { $^1H$ } NMR ( $CDCl_3$ ):  $\delta_C$  150.9 (C), 150.1 (2 $\times$ CH), 144.0 (C), 141.9 (C), 137.2 (C), 134.9 (C), 129.5 (2 $\times$ CH), 128.5 (CH), 125.9 (2 $\times$ CH), 122.5 (2 $\times$ CH), 118.3 (CH), 112.6 (C3), 61.3 (C6), 43.2 (C5), 40.0 (C4), 28.5 (C5a,b), 21.3 (Ph-CH<sub>3</sub>). FTIR (neat, *cis*): 3083, 3028, 2958, 2926, 2872, 1648, 1602, 1539, 1510, 1488, 1464, 1438, 1415, 1389, 1370, 1324, 1267, 1216, 1179, 1117, 1066, 1041, 992; *trans*: 3026, 2957, 2928, 2866, 1602, 1537, 1513, 1490, 1462, 1438, 1415, 1370, 1328, 1274, 1216, 1183, 1170. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{22}H_{23}N_3$ : 330.1965. Found: 330.1964.

**Methyl-3-(5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)acrylate (5c).** Yield 89 mg, 87%; *cis/trans* 5:95, *trans* - a colorless solid; mp 127.8–128.4 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.69 (d,  $^3J = 4.9$ , 2H, 2×CH), 7.72 (d,  $^3J = 15.9$ , 1H, CH), 7.51 (d,  $^3J = 4.9$ , 2H, 2×CH), 6.01 (d,  $^3J = 15.9$ , 1H, CH), 3.98 (s, 2H, H6), 3.77 (s, 3H,  $\text{OCH}_3$ ), 2.90 (s, 2H, H4), 1.38 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  167.5 (C=O), 153.0 (C), 150.2 (2×CH), 146.4 (CH), 140.7 (C), 135.5 (2×CH), 122.7 (C), 116.2 (CH), 110.0 (C3), 61.3 (C6), 51.5 ( $\text{OCH}_3$ ), 43.3 (C5), 40.0 (C4), 28.4 (C5a,b). FTIR (neat): 2963, 2940, 2909, 2887, 2871, 2832, 1701, 1632, 1600, 1557, 1534, 1489, 1437, 1428, 1418, 1326, 1308, 1287, 1266, 1233, 1193, 1068, 1020, 989. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2$ : 298.1550. Found: 298.1546. CCDC 1497729

**3-(5,5-Dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)prop-2-en-1-ol (5d).** **5c** (100 mg, 0.336 mmol) was dissolved in anhydrous DCM (4 mL). The reaction mixture was cooled down to 0 °C and 1 M DIBAL-H in DCM (1.0 mL, 3 equiv.) was added dropwise within 10 min. The colorless mixture was stirred at 0 °C for 1 h and then the reaction was quenched with 1 M HCl (to pH 7). Water was added (10 mL) and the product was extracted with DCM (3×7 mL). Combined organic phases were washed with brine (15 mL), dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Column chromatography (MeOH/DCM 1:15) afforded 70 mg, 77% of a colorless solid; mp 153.7–154.8 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.50 (d,  $^3J = 4.8$ , 2H, 2×CH), 7.47 (d,  $^3J = 4.8$ , 2H, 2×CH), 6.54 (d,  $^3J = 15.9$ , 1H, CH), 5.92 (dt,  $^3J = 15.9$ , 5.7, 1H, CH), 4.23 (d,  $^3J = 5.7$ , 2H,  $\text{CH}_2\text{OH}$ ), 3.87 (s, 2H, H6), 3.72 (bs, 1H, OH), 2.76 (s, 2H, H4), 1.28 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  150.3 (C), 149.7 (2×CH), 144.4 (CH), 142.1 (C), 129.3 (C), 122.5 (2×CH), 121.1 (CH), 111.8 (C3), 63.5

(CH<sub>2</sub>OH), 61.2 (C6), 43.2 (C5), 39.7 (C4), 28.4 (C5a,b). FTIR (neat): 3245, 3052, 3015, 2968, 2953, 2923, 2896, 2871, 2849, 1606, 1538, 1436, 1418, 1372, 1347, 1323, 1296, 1273, 1212, 1183, 1126, 1088, 1064, 1002. HRMS (ESI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>16</sub>H<sub>20</sub>N<sub>3</sub>O: 270.1601. Found: 270.1603.

**Pyridin-4-yl Substituted Products at C2: Sonogashira Cross-Coupling and Related Products.** **4c** (100 mg, 0.295 mmol), relevant acetylene (2 equiv. for **5e,f** and 6 equiv. for **5g**), CuI (10 mol%), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mol%) and Et<sub>3</sub>N (3 equiv.) were dissolved in anhydrous MeCN (2.5 mL). The mixture was stirred at 70 °C under an argon atmosphere for 1 h. MeCN was evaporated and the crude products were purified and finally crystallized from MeCN.

**3-((4-Methoxyphenyl)ethynyl)-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (**5e**).** Column chromatography (EtOAc/DCM 2:1) afforded 80 mg, 80% of yellow solid; mp 127.2–127.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 7.75–8.70 (m, 4H, 4×CH), 7.44 (d, <sup>3</sup>*J* = 8.7, 2H, 2×CH), 6.88 (d, <sup>3</sup>*J* = 8.7, 2H, 2×CH), 3.92 (s, 2H, H6), 3.80 (s, 3H, OCH<sub>3</sub>), 2.84 (s, 2H, H4), 1.32 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ<sub>C</sub> 159.7 (C), 152.2 (C), 149.8 (2×CH), 149.6 (C), 140.5 (C), 132.7 (2×CH), 120.5 (2×CH), 115.6 (C), 114.2 (2×CH), 96.3 (–C≡C–), 93.3 (–C≡C–), 80.1 (C3), 61.8 (C6), 55.4 (OCH<sub>3</sub>), 43.1 (C5), 38.7 (C4), 28.2 (C5a,b). FTIR (neat): 3027, 2958, 2940, 2906, 2869, 2849, 2838, 2220, 1600, 1565, 1504, 1462, 1437, 1420, 1374, 1367, 1326, 1283, 1246, 1177, 1165, 1106, 1019, 991. HRMS (ESI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O: 344.1757. Found: 344.1754.

**5,5-Dimethyl-3-(phenylethynyl)-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (**5f**).** Column chromatography (EtOAc) afforded 81 mg, 88% of yellow solid; mp 116.0–

116.9 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.85–8.55 (m, 4H, 4 $\times$ CH), 7.44–7.52 (m, 2H, 2 $\times$ CH), 7.28–7.36 (m, 3H, 3 $\times$ CH), 3.89 (s, 2H, H6), 2.82 (s, 2H, H4), 1.30 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  152.4 (C), 150.0 (2 $\times$ CH), 149.9 (C), 140.8 (C), 131.3 (2 $\times$ CH), 128.5 (2 $\times$ CH), 128.3 (CH), 123.5 (C), 120.3 (2 $\times$ CH), 96.0 ( $-\text{C}\equiv\text{C}-$ ), 93.5 ( $-\text{C}\equiv\text{C}-$ ), 81.6 (C3), 61.8 (C6), 43.1 (C5), 38.7 (C4), 28.3 (C5a,b). FTIR (neat): 3071, 3023, 2955, 2923, 2877, 2849, 2219, 1596, 1569, 1540, 1486, 1466, 1448, 1435, 1418, 1372, 1312, 1301, 1264, 1250, 1225, 1174, 1158, 1066, 989. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{21}\text{H}_{19}\text{N}_3$ : 314.1657. Found: 314.1647. CCDC 1497730

**5,5-Dimethyl-2-(pyridin-4-yl)-3-((trimethylsilyl)ethynyl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (5g).** Column chromatography (EtOAc/DCM 1:1) afforded 458 mg, 95% of a colorless solid; mp 132.9–133.1 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.64 (bs, 2H, 2 $\times$ CH), 8.00 (bs, 2H, 2 $\times$ CH), 3.82 (s, 2H, H6), 2.73 (s, 2H, H4), 1.22 (s, 6H, H5a,b), 0.20 (s, 9H, TMS).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  152.5 (C), 150.1 (C), 149.7 (2 $\times$ CH), 140.6 (C), 120.6 (2 $\times$ CH), 98.9 ( $-\text{C}\equiv\text{C}-$ ), 97.4 ( $-\text{C}\equiv\text{C}-$ ), 96.0 (C3), 61.6 (C6), 43.0 (C5), 38.5 (C4), 28.1 (C5a,b), 0.0 (TMS). FTIR (neat): 3043, 3031, 2962, 2934, 2910, 2877, 2848, 2153, 1597, 1535, 1487, 1465, 1450, 1432, 1418, 1370, 1316, 1273, 1247, 1216, 1177, 1066, 988. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{18}\text{H}_{23}\text{N}_3\text{Si}$ : 310.1734. Found: 310.1729.

**3-Ethynyl-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (5h).** **5g** (500 mg, 1.62 mmol) was dissolved in anhydrous MeOH (10 mL).  $\text{K}_2\text{CO}_3$  (223 mg, 1.62 mmol) was added and the solution was stirred for 0.5 h at rt under an argon atmosphere. The solid residue was filtered and washed with MeOH (3 $\times$ 5 mL). The solvent was evaporated and the crude product was purified by column chromatography

(EtOAc) affording 383 mg, 97% of a colorless solid; mp 140.6–141.0 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.54 (d,  $^3J = 4.6$ , 2H, 2 $\times$ CH), 7.93 (d,  $^3J = 4.6$ , 2H, 2 $\times$ CH), 7.26 (s, 1H,  $\equiv\text{CH}$ ), 3.84 (s, 2H, H6), 2.72 (s, 2H, H4), 1.23 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  152.5 (C), 150.8 (C), 149.8 (2 $\times$ CH), 140.7 (C), 120.4 (2 $\times$ CH), 94.8 ( $-\text{C}\equiv\text{CH}$ ), 81.8 (C3), 77.4 ( $-\text{C}\equiv\text{CH}$ ), 61.6 (C6), 43.0 (C5), 38.4 (C4), 28.1 (C5a,b). FTIR (neat): 3095, 2957, 2936, 2911, 2872, 1602, 1533, 1485, 1466, 1445, 1431, 1421, 1401, 1370, 1322, 1266, 1236, 1216, 1178, 1066, 996. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{15}\text{H}_{15}\text{N}_3$ : 238.1339. Found: 238.1333.

**Preparation of 5i and 5j.** **5h** (100 mg, 0.421 mmol), aryl iodide (1.2 equiv.), CuI (10 mol%),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (5 mol%) and  $\text{Et}_3\text{N}$  (3 equiv.) were dissolved in anhydrous MeCN (2.5 mL). The mixture was stirred at 70 °C under an argon atmosphere for 1 h. MeCN was evaporated and the crude products were purified and finally crystallized from MeCN.

**5,5-Dimethyl-3-(pyridin-2-ylethynyl)-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (5i).** Column chromatography (MeOH/DCM 1:15) afforded 110 mg, 83% of light yellow solid; mp 105.5–106.2 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.59–8.63 (m, 1H, CH), 8.11 (bs, 4H, 4 $\times$ CH), 7.62–7.70 (m, 1H, CH), 7.42–7.48 (m, 1H, CH), 7.18–7.24 (m, 1H, CH), 3.94 (s, 2H, H6), 2.87 (s, 2H, H4), 1.32 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  153.0 (C), 150.8 (C), 150.2 (CH), 150.0 (2 $\times$ CH), 143.7 (C), 140.5 (C), 136.3 (CH), 127.0 (CH), 122.8 (CH), 120.8 (2 $\times$ CH), 95.2 ( $-\text{C}\equiv\text{C}-$ ), 93.0 ( $-\text{C}\equiv\text{C}-$ ), 81.8 (C3), 61.9 (C6), 43.3 (C5), 38.9 (C4), 28.3 (C5a,b). FTIR (neat): 3069, 3035, 2993, 2955, 2929, 2878, 2852, 2222, 1598, 1580, 1559, 1541, 1491, 1462, 1439, 1420, 1389, 1371, 1333, 1303, 1280, 1265, 1217, 1175,

1145, 1091, 1064, 1039, 986. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{20}H_{18}N_4$ : 315.1604.  
Found: 315.1605.

**5,5-Dimethyl-3-((4-nitrophenyl)ethynyl)-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (5j).** Column chromatography (EtOAc) afforded 128 mg, 85% of yellow solid; mp 170.9–171.1 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.50–8.60 (m, 2H, 2 $\times$ CH), 8.21 (d,  $^3J = 8.8$ , 2H, 2 $\times$ CH), 7.90–8.00 (m, 2H, 2 $\times$ CH), 7.59 (d,  $^3J = 8.8$ , 2H, 2 $\times$ CH), 3.99 (s, 2H, H6), 2.90 (s, 2H, H4), 1.38 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  152.9 (C), 150.6 (C), 150.0 (2 $\times$ CH), 146.8 (C), 140.4 (C), 131.7 (2 $\times$ CH), 130.5 (C), 123.8 (2 $\times$ CH), 119.2 (2 $\times$ CH), 95.0 ( $-C\equiv C-$ ), 91.9 ( $-C\equiv C-$ ), 87.6 (C3), 61.9 (C6), 43.2 (C5), 38.7 (C4), 28.2 (C5a,b). FTIR (neat): 3038, 2958, 2944, 2905, 2871, 2847, 2212, 1593, 1562, 1541, 1508, 1472, 1453, 1434, 1416, 1400, 1375, 1338, 1304, 1291, 1217, 1172, 1103, 1092, 989. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{21}H_{18}N_4O_2$ : 359.1503. Found: 359.1496.

**Pyridin-4-yl Substituted Products at C2: Suzuki Cross-Coupling Products. 4b** (100 mg, 0.342 mmol), relevant boronic acid (1.5 equiv.),  $Pd(PPh_3)_4$  (2–5 mol%) and 2 M aq.  $K_2CO_3$  (3 equiv.) were dissolved in DMF (4 mL) and the mixture was stirred at 110 °C for 1 – 2 h. Then, DMF was evaporated and the crude product was purified and finally crystallized from MeCN.

**3-(4-Methoxyphenyl)-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (5k).** Column chromatography (EtOAc) afforded 92 mg, 85% of light yellow solid; mp 114.2–114.7 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.50 (d,  $^3J = 6.0$ , 2H, 2 $\times$ CH), 7.42 (d,  $^3J = 6.0$ , 2H, 2 $\times$ CH), 7.15 (d,  $^3J = 8.6$ , 2H, 2 $\times$ CH), 6.88 (d,  $^3J = 8.6$ , 2H, 2 $\times$ CH), 3.98 (s, 2H, H6), 3.83 (s, 3H,  $OCH_3$ ), 2.77 (s, 2H, H4), 1.35 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  158.7

(C), 150.0 (2×CH), 149.5 (C), 145.0 (C), 142.2 (C), 130.1 (2×CH), 125.7 (C), 122.3 (2×CH), 114.3 (C3), 114.4 (2×CH), 61.6 (C6), 55.5 (OCH<sub>3</sub>), 43.2 (C5), 38.9 (C4), 28.5 (C5a,b). FTIR (neat): 3025, 2956, 2929, 2885, 2869, 2843, 1599, 1565, 1542, 1504, 1465, 1450, 1435, 1412, 1389, 1370, 1322, 1292, 1283, 1241, 1213, 1177, 1121, 1029, 1012, 986. Anal. Calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.01; H, 6.61; N, 12.87.

**4-(5,5-Dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)phenol (5I).**

Column chromatography (MeOH/EtOAc 1:6) afforded 101 mg, 97% of a colorless solid; mp 273.4–274.2 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 8.50 (d, <sup>3</sup>*J* = 6.3, 2H, 2×CH), 7.41 (d, <sup>3</sup>*J* = 6.3, 2H, 2×CH), 7.07 (d, <sup>3</sup>*J* = 8.6, 2H, 2×CH), 6.79 (d, <sup>3</sup>*J* = 8.6, 2H, 2×CH), 3.99 (s, 2H, H6), 3.40 (bs, 1H, OH), 2.77 (s, 2H, H4), 1.30 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (DMSO-*d*<sub>6</sub>): δ<sub>C</sub> 157.1 (C), 150.6 (C), 148.5 (2×CH), 145.7 (C), 142.6 (C), 130.5 (2×CH), 124.2 (C), 122.4 (2×CH), 116.5 (2×CH), 115.2 (C3), 61.5 (C6), 43.6 (C5), 38.7 (C4), 28.6 (C5a,b). FTIR (neat): 2960, 2869, 2762, 2642, 2556, 1735, 1607, 1569, 1546, 1508, 1463, 1435, 1418, 1366, 1323, 1301, 1279, 1229, 1209, 1170, 1117, 1091, 1062, 1009, 987. HRMS (ESI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O: 306.1601. Found: 306.1598.

**5,5-Dimethyl-3-phenyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (5m).**

Column chromatography (EtOAc) afforded 97 mg, 98% of a colorless solid; mp 82.6–83.0 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 8.50 (d, <sup>3</sup>*J* = 6.0, 2H, 2×CH), 7.43 (d, <sup>3</sup>*J* = 6.0, 2H, 2×CH), 7.18–7.36 (m, 5H, 5×CH), 3.99 (s, 2H, H6), 2.80 (s, 2H, H4), 1.35 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ<sub>C</sub> 150.0 (2×CH), 149.6 (C), 145.3 (C), 142.0 (C), 133.4 (C), 128.8 (2×CH), 128.8 (CH), 126.8 (2×CH), 122.4 (2×CH), 115.2 (C3), 61.6 (C6), 43.2 (C5), 39.0 (C4), 28.5 (C5a,b). FTIR (neat): 3039, 2960, 2951, 2905, 2874, 1601, 1575, 1542, 1494, 1486, 1465, 1420,



1388, 1367, 1304, 1278, 1248, 1224, 1180, 1119, 1171, 990. HRMS (ESI)  $m/z$ :  $[M + H]^+$

Calcd. for  $C_{19}H_{19}N_3$ : 290.1652. Found: 290.1657.

**3-(4-Chlorophenyl)-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-**

**b]pyrazole (5n).** Column chromatography (EtOAc) afforded 102 mg, 92% of a colorless solid; mp 124.4–124.8 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.52 (d,  $^3J = 6.0$ , 2H, 2×CH), 7.39 (d,  $^3J = 6.0$ , 2H, 2×CH), 7.30 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.15 (d,  $^3J = 8.4$ , 2H, 2×CH), 3.99 (s, 2H, H6), 2.79 (s, 2H, H4), 1.36 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  150.0 (2×CH), 149.6 (C), 145.3 (C), 141.8 (C), 132.7 (C), 131.8 (C), 130.0 (2×CH), 129.0 (2×CH), 122.4 (2×CH), 114.0 (C3), 61.5 (C6), 43.2 (C5), 38.9 (C4), 28.4 (C5a,b). FTIR (neat): 3049, 3035, 2955, 2928, 2903, 2869, 2852, 1597, 1539, 1489, 1462, 1435, 1414, 1398, 1369, 1319, 1281, 1265, 1215, 1179, 1119, 1103, 1088, 1014, 987. Anal. Calcd. for  $C_{19}H_{18}N_3Cl$ : C, 70.47; H, 5.60; N, 12.98. Found: C, 70.19; H, 5.54; N, 12.60. CCDC 1497731

**3-(4-Fluorophenyl)-5,5-dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-**

**b]pyrazole (5o).** Column chromatography (MeOH/DCM 1:15) afforded 98 mg, 93% of a colorless solid; mp 130.7–132.0 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.51 (d,  $^3J = 6.0$ , 2H, 2×CH), 7.40 (d,  $^3J = 6.0$ , 2H, 2×CH), 7.16–7.21 (m, 2H, 2×CH), 7.00–7.05 (m, 2H, 2×CH), 3.99 (s, 2H, H6), 2.77 (s, 2H, H4), 1.36 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  161.9 (d,  $J_{C,F} = 246.2$ , C), 149.9 (2×CH), 149.5 (C), 145.2 (C), 142.0 (C), 130.5 (d,  $J_{C,F} = 8.0$ , 2×CH), 129.3 (d,  $J_{C,F} = 3.5$ , C), 122.3 (2×CH), 115.8 (d,  $J_{C,F} = 21.5$ , 2×CH), 114.3 (C3), 61.6 (C6), 43.3 (C5), 38.9 (C4), 28.5 (C5a,b). FTIR (neat): 3032, 2958, 2930, 2896, 2869, 1598, 1566, 1542, 1503, 1437, 1411, 1387, 1370, 1323, 1304, 1287, 1256, 1181, 1161, 1117, 1094, 987. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{19}H_{18}N_3F$ : 308.1558. Found: 308.1553.

**4-(5,5-Dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)benzaldehyde (5p).** Column chromatography (EtOAc/DCM 2:1) afforded 98 mg, 90% of a colorless solid; mp 129.5–130.9 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  9.95 (s, 1H, HC=O), 8.50 (d,  $^3J$  = 6.2, 2H, 2×CH), 7.79 (d,  $^3J$  = 8.4, 2H, 2×CH), 7.27 – 7.39 (m, 4H, 4×CH), 3.98 (s, 2H, H6), 2.82 (s, 2H, H4), 1.34 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  191.6 (HC=O), 150.0 (C), 150.0 (2×CH), 145.7 (C), 141.5 (C), 139.7 (C), 134.5 (C), 130.1 (2×CH), 128.8 (2×CH), 122.5 (2×CH), 113.8 (C3), 61.4 (C6), 43.2 (C5), 39.1 (C4), 28.3 (C5a,b). FTIR (neat): 3030, 2959, 2929, 2872, 2851, 2831, 2732, 1699, 1604, 1570, 1543, 1490, 1465, 1438, 1414, 1390, 1371, 1321, 1305, 1291, 1213, 1168, 1100, 1066, 987. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{20}\text{H}_{20}\text{ON}_3$ : 318.1601. Found: 318.1602.

**4-(5,5-Dimethyl-2-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)benzonitrile**

**(5q).** Column chromatography (MeOH/DCM 1:20) afforded 99 mg, 92% of light orange solid; mp 158.0–158.6 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.56 (d,  $^3J$  = 4.8, 2H, 2×CH), 7.60 (d,  $^3J$  = 8.4, 2H, 2×CH), 7.38 (d,  $^3J$  = 4.8, 2H, 2×CH), 7.31 (d,  $^3J$  = 8.4, 2H, 2×CH), 4.01 (s, 2H, H6), 2.84 (s, 2H, H4), 1.38 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  150.3 (2×CH), 150.2 (C), 145.8 (C), 141.6 (C), 138.4 (C), 132.7 (2×CH), 129.0 (2×CH), 122.7 (2×CH), 119.0 (C), 113.5 (C), 110.3 (C3), 61.6 (C6), 43.4 (C5), 39.2 (C4), 28.5 (C5a,b). FTIR (neat): 3048, 3021, 2960, 2933, 2901, 2873, 2221, 1604, 1565, 1540, 1491, 1461, 1437, 1415, 1391, 1370, 1320, 1285, 1269, 1215, 1180, 1129, 1097, 1067, 987. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{20}\text{H}_{18}\text{N}_4$ : 315.1604. Found: 315.1600.

**5,5-Dimethyl-2,3-di(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (5r).** Column chromatography (MeOH/EtOAc 1:6) afforded 97 mg, 98% of a colorless solid; mp 155.5–

156.4 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.58 (d,  $^3J = 6.0$ , 2H, 2 $\times$ CH), 8.53 (d,  $^3J = 6.0$ , 2H, 2 $\times$ CH), 7.41 (d,  $^3J = 6.0$ , 2H, 2 $\times$ CH), 7.13 (d,  $^3J = 6.0$ , 2H, 2 $\times$ CH), 4.01 (s, 2H, H<sub>6</sub>), 2.87 (s, 2H, H<sub>4</sub>), 1.38 (s, 6H, H<sub>5a,b</sub>).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  150.5 (C), 150.3 (2 $\times$ CH), 150.3 (2 $\times$ CH), 146.1 (C), 141.5 (C), 141.4 (C), 123.0 (2 $\times$ CH), 122.7 (2 $\times$ CH), 112.4 (C<sub>3</sub>), 61.6 (C<sub>6</sub>), 43.4 (C<sub>5</sub>), 39.4 (C<sub>4</sub>), 28.5 (C<sub>5a,b</sub>). FTIR (neat): 3031, 2964, 2943, 2870, 1597, 1532, 1489, 1408, 1364, 1283, 1221, 1175, 1105, 989. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{18}\text{H}_{18}\text{N}_4$ : 291.1604. Found: 291.1605.

**Quinolin-4-yl and 2-Cyanophenyl Substituted Products at C2: Suzuki Cross-Coupling and Related Products.** **4d** or **4e** (100 mg), relevant boronic acid (1.5 equiv.),  $\text{Pd}(\text{PPh}_3)_4$  (2-5 mol%, 7.5 mol% for **5z**) and 2 M aq.  $\text{K}_2\text{CO}_3$  (3 equiv.) were dissolved in DMF (4 mL) and the mixture was stirred at 110 °C for 1 - 2 h (15 h for **5z**). Then, DMF was evaporated and the crude product was purified and finally crystallized from MeCN.

**4-(3-(4-Methoxyphenyl)-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)quinoline (5s).** Column chromatography (MeOH/ $\text{CHCl}_3$  1:20) afforded 93 mg, 86% of colorless solid; mp 111.5–111.9 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.86 (d,  $^3J = 4.4$ , 1H, CH), 8.11 (t,  $^3J = 8.3$ , 2H, 2 $\times$ CH), 7.66 (ddd,  $^3J = 8.3$ , 6.9, 1.3, 1H, CH), 7.40 (ddd,  $^3J = 8.2$ , 6.9, 1.1, 1H, CH), 7.36 (d,  $^3J = 4.4$ , 1H, CH), 6.92–6.96 (m, 2H, 2 $\times$ CH), 6.66–6.71 (m, 2H, 2 $\times$ CH), 4.05 (s, 2H, H<sub>6</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 2.94 (s, 2H, H<sub>4</sub>), 1.42 (s, 6H, H<sub>5a,b</sub>).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  158.1 (C), 150.2 (CH), 149.1 (C), 149.0 (C), 143.8 (C), 141.1 (C), 129.7 (CH), 129.4 (CH), 128.9 (2 $\times$ CH), 127.2 (C), 126.9 (CH), 126.7 (CH), 125.6 (C), 122.7 (CH), 115.7 (C<sub>3</sub>), 114.2 (2 $\times$ CH), 61.6 (C<sub>6</sub>), 55.4 (OCH<sub>3</sub>), 43.4 (C<sub>5</sub>), 39.7 (C<sub>4</sub>), 28.7 (C<sub>5a,b</sub>). FTIR (neat): 2957, 2935, 2890, 2870, 2836, 1589, 1576, 1555, 1506, 1465, 1440, 1419,

1379, 1317, 1291, 1277, 1245, 1177, 1132, 1118, 1040, 1024, 1010. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{24}H_{23}N_3O$ : 370.1914. Found: 370.1910.

**2-(3-(4-Methoxyphenyl)-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-**

**yl)benzonitrile (5t).** Column chromatography (DCM to EtOAc/DCM 1:20) afforded 95 mg, 87% of colorless solid; mp 161.7–162.9 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H$  7.63–7.68 (m, 1H, CH), 7.45–7.53 (m, 2H, 2×CH), 7.34–7.39 (m, 1H, CH), 6.96–7.02 (m, 2H, 2×CH), 6.76–6.81 (m, 2H, 2×CH), 3.99 (s, 2H, H6), 3.75 (s, 3H,  $OCH_3$ ), 2.85 (s, 2H, H4), 1.35 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta_C$  158.0 (C), 148.9 (C), 143.7 (C), 138.1 (C), 133.5 (CH), 132.3 (CH), 131.0 (CH), 128.8 (2×CH), 127.9 (CH), 125.5 (C), 118.4 (C), 114.9 (C3), 114.1 (2×CH), 112.5 (CN), 61.3 (C6), 55.1 ( $OCH_3$ ), 43.0 (C5), 39.1 (C4), 28.4 (C5a,b). FTIR (neat): 3012, 2965, 2937, 2912, 2885, 2874, 2838, 2229, 1618, 1600, 1578, 1562, 1511, 1504, 1465, 1454, 1443, 1426, 1408, 1390, 1372, 1325, 1297, 1289, 1246, 1179, 1111, 1083, 1034, 985. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{22}H_{22}N_3O$ : 344.1757. Found: 344.1759.

**2-(3-(4-Hydroxyphenyl)-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-**

**yl)benzonitrile (5u).** Column chromatography (EtOAc/DCM 1:6) afforded 96 mg, 92% of colorless solid; mp 235.4–236.9 °C.  $^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta_H$  9.33 (s, 1H, OH), 7.82–7.87 (m, 1H, CH), 7.62–7.69 (m, 1H, CH), 7.50–7.55 (m, 1H, CH), 7.40–7.44 (m, 1H, CH), 6.85 (d,  $^3J = 8.0$ , 2H, 2×CH), 6.65 (d,  $^3J = 8.0$ , 2H, 2×CH), 3.96 (s, 2H, H6), 2.85 (s, 2H, H4), 1.28 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR (100 MHz,  $DMSO-d_6$ ):  $\delta_C$  155.6 (C), 147.7 (C), 143.3 (CH), 137.9 (C), 133.6 (CH), 132.8 (CH), 130.8 (CH), 128.4 (2×CH), 128.3 (2×CH), 123.4 (C), 118.2 (C), 115.5 (C), 114.3 (C3), 111.6 (CN), 60.5 (C6), 42.8 (C5), 38.3 (C4), 27.7 (C5a,b).

FTIR (KBr): 3418, 2963, 2936, 2876, 2223, 1614, 1600, 1572, 1554, 1504, 1465, 1453, 1432, 1416, 1389, 1371, 1334, 1324, 1293, 1280, 1268, 1222, 1172, 1101, 1083, 1036, 989. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{21}H_{20}N_3O$ : 330.1601. Found: 330.1603.

**4-(3-(4-Chlorophenyl)-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-**

**yl)quinoline (5v).** Column chromatography (EtOAc) afforded 105 mg, 96% of an off-white solid; mp 119.3–120.2 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H$  8.88 (d,  $^3J = 4.4$ , 1H, CH), 8.14 (d,  $^3J = 8.4$ , 1H, CH), 8.05 (d,  $^3J = 8.3$ , 1H, CH), 7.65–7.71 (m, 1H, CH), 7.42 (t,  $^3J = 7.2$ , 1H, CH), 7.35 (d,  $^3J = 4.4$ , 1H, CH), 7.10 (d,  $^3J = 8.5$ , 2H, 2×CH), 6.94 (d,  $^3J = 8.5$ , 2H, 2×CH), 4.06 (s, 2H, H6), 2.95 (s, 2H, H4), 1.42 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta_C$  150.0 (CH), 149.1 (C), 148.9 (C), 144.2 (C), 140.6 (C), 131.9 (C), 131.6 (C), 129.7 (CH), 129.4 (CH), 128.8 (2×CH), 128.7 (2×CH), 126.9 (C), 126.8 (CH), 126.6 (CH), 122.5 (CH), 114.8 (C3), 61.5 (C6), 43.3 (C5), 39.6 (C4), 28.5 (C5a,b). FTIR (neat): 2959, 2901, 2886, 2869, 1583, 1544, 1511, 1490, 1467, 1436, 1417, 1381, 1349, 1317, 1304, 1280, 1177, 1152, 1095, 1012, 970. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{23}H_{20}N_3Cl$ : 374.1419. Found: 374.1418.

**4-(5,5-Dimethyl-3-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)quinoline**

**(5x).** Column chromatography (MeOH/DCM 1:10) afforded 87 mg, 87% of colorless solid; mp 173.0–173.6 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H$  8.93 (d,  $^3J = 4.4$ , 1H, CH), 8.32 (d,  $^3J = 6.1$ , 2H, 2×CH), 8.16 (d,  $^3J = 8.4$ , 1H, CH), 7.95 (d,  $^3J = 8.4$ , 1H, CH), 7.69 (t,  $^3J = 7.3$ , 1H, CH), 7.42 (t,  $^3J = 7.6$ , 1H, CH), 7.39 (d,  $^3J = 4.4$ , 1H, CH), 6.88 (d,  $^3J = 6.1$ , 2H, 2×CH), 4.08 (s, 2H, H6), 3.03 (s, 2H, H4), 1.45 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta_C$  150.2 (2×CH), 150.1 (2×CH), 149.9 (C), 149.1 (C), 145.4 (C), 140.9 (C), 140.4 (C), 130.0 (CH),

129.7 (CH), 127.1 (CH), 126.9 (C), 126.3 (CH), 122.6 (C), 121.6 (2×CH), 113.4 (C3), 61.7 (C6), 43.6 (C5), 40.1 (C4), 28.6 (C5a,b). FTIR (neat): 2961, 2929, 2885, 2870, 1596, 1554, 1532, 1511, 1494, 1467, 1439, 1408, 1382, 1371, 1354, 1316, 1309, 1284, 1258, 1222, 1179, 1147, 1132, 1091, 1067, 990. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{22}H_{20}N_4$ : 341.1761. Found: 341.1757. CCDC 1497732

**2-(5,5-Dimethyl-3-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)benzonitrile (5y).** Column chromatography (EtOAc/DCM 2:1) afforded 95 mg, 96% of colorless solid; mp 155.8–157.1 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H$  8.40–8.44 (m, 2H, 2×CH), 7.69–7.72 (m, 1H, CH), 7.56–7.62 (m, 1H, CH), 7.49–7.52 (m, 1H, CH), 7.44–7.49 (m, 1H, CH), 6.92–6.96 (m, 2H, 2×CH), 4.02 (s, 2H, H6), 2.93 (s, 2H, H4), 1.38 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta_C$  150.1 (2×CH), 149.9 (C), 145.3 (C), 141.1 (C), 137.6 (CH), 133.7 (CH), 132.8 (CH), 131.0 (CH), 128.7 (C), 121.7 (2×CH), 118.1 (C), 112.8 (C3), 112.8 (CN), 61.4 (C6), 43.3 (C5), 39.7 (C4), 28.5 (C5a,b). FTIR (neat): 2966, 2888, 2875, 2855, 2230, 1604, 1573, 1560, 1543, 1493, 1464, 1454, 1440, 1426, 1412, 1392, 1373, 1328, 1320, 1303, 1248, 1181, 1081, 990. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{20}H_{19}N_4$ : 315.1604. Found: 315.1605.

**4,4'-(5,5-Dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2,3-diyl)diquinoline (5z).** Add JohnPhos (13 mg, 0.044 mmol, 13 mol%) to get higher yield. Column chromatography (MeOH/DCM 1:20) afforded 59 mg, 52% of an off-white solid; mp 206.8–207.1 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H$  9.09 (s, 1H, CH), 8.60 (d,  $^3J = 4.5$ , 1H, CH), 8.34 (dd,  $^3J = 8.5$ , 1.4, 1H, CH), 8.25 (s, 1H, CH), 8.02 (d,  $^3J = 8.5$ , 1H, CH), 7.89–7.94 (m, 1H, CH), 7.66–7.72 (m, 1H, CH), 7.61 (ddd,  $^3J = 8.5$ , 6.8, 1.4, 1H, CH), 7.46–7.51 (m, 2H,

2×CH), 7.37 (ddd,  $^3J = 8.5, 6.8, 1.4$ , 1H, CH), 7.08 (d,  $^3J = 4.5$ , 1H, CH), 4.16 (s, 2H, H6), 2.76 (s, 2H, H4), 1.41 (s, 6H, H5a,b).  $^{13}\text{C} \{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  151.7 (CH), 151.0 (C), 149.6 (CH), 148.8 (C), 146.0 (C), 144.0 (CH), 139.6 (C), 134.3 (C), 130.4 (CH), 129.6 (CH), 129.1 (CH), 128.3 (C), 128.0 (CH), 127.1 (CH), 126.5 (C), 126.5 (CH), 126.3 (CH), 124.4 (C), 124.3 (CH), 121.9 (CH), 110.7 (C3), 61.7 (C6), 43.4 (C5), 39.0 (C4), 28.3 (C5a,b). FTIR (neat): 3060, 3038, 2959, 2930, 2894, 2869, 1619, 1585, 1564, 1502, 1492, 1464, 1442, 1418, 1396, 1362, 1319, 1294, 1282, 1225, 1211, 1180, 1134, 1116, 999. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{26}\text{H}_{22}\text{N}_4$ : 391.1917. Found: 391.1911.

### Pyridin-2-yl and 6-Methylpyridin-2-yl Substituted Products at C2: Halogenations.

#### 3-Chloro-5,5-dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (6a). 3d

(1.00 g, 4.69 mmol) was dissolved in anhydrous  $\text{CHCl}_3$  (20 mL), NCS (1.25 g, 9.38 mmol, 2 equiv.) was added in few portions and the reaction mixture was stirred for 16 h at rt. Then, DCM (15 mL) was added and the mixture was washed with water (3×20 mL). The collected organic phases were dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Column chromatography (EtOAc) afforded 789 mg, 68% of light yellow solid; mp 90.8–91.6 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.69–8.74 (m, 1H, CH), 7.92–7.98 (m, 1H, CH), 7.69–7.78 (m, 1H, CH), 7.19–7.26 (m, 1H, CH), 3.97 (s, 2H, H6), 2.76 (s, 2H, H4), 1.34 (s, 6H, H5a,b).  $^{13}\text{C} \{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  151.6 (C), 149.8 (CH), 149.8 (C), 143.8 (C), 136.4 (CH), 122.5 (CH), 121.8 (CH), 102.8 (C3), 62.2 (C6), 43.1 (C5), 38.2 (C4), 28.2 (C5a,b). FTIR (neat): 2962, 2948, 2909, 2878, 2851, 1588, 1567, 1503, 1446, 1411, 1355, 1318, 1259, 1195, 1180, 1149, 1123, 1113, 1088, 1028, 989. Anal. Calcd. for  $\text{C}_{13}\text{H}_{14}\text{N}_3\text{Cl}$ : C, 63.03; H, 5.70; N, 16.96. Found: C, 63.04; H, 5.76; N, 17.01.

**3-Bromo-5,5-dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (6b). 3d**

(1.00 g, 4.69 mmol) was dissolved in anhydrous  $\text{CHCl}_3$  (20 mL), NBS (960 mg, 5.39 mmol, 1.15 equiv.) was added in few portions and the reaction mixture was stirred for 30 min at rt. Then, DCM (20 mL) was added and the mixture was washed with 10% aq.  $\text{Na}_2\text{S}_2\text{O}_5$  (10 mL) and water (3×20 mL). The collected organic phases were dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Column chromatography (EtOAc/DCM 1:2) afforded 1.12 g, 82% of light yellow solid; mp 119.1–119.6 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.68–8.72 (m, 1H, CH), 7.93–7.98 (m, 1H, CH), 7.71–7.76 (m, 1H, CH), 7.20–7.25 (m, 1H, CH), 3.99 (s, 2H, H6), 2.73 (s, 2H, H4), 1.33 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  151.7 (C), 151.1 (C), 149.7 (CH), 146.2 (C), 136.4 (CH), 122.6 (CH), 122.0 (CH), 86.4 (C3), 62.3 (C6), 43.0 (C5), 38.5 (C4), 28.3 (C5a,b). FTIR (neat): 2967, 2954, 2876, 1588, 1565, 1500, 1464, 1446, 1435, 1409, 1352, 1323, 1275, 1259, 1185, 1150, 1111, 1087, 1015. Anal. Calcd. for  $\text{C}_{13}\text{H}_{14}\text{N}_3\text{Br}$ : C, 53.44; H, 4.83; N, 14.38. Found: C, 53.43; H, 4.78; N, 14.17. CCDC 1497733

**3-Iodo-5,5-dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (6c). 3d**

(1.00 g, 4.69 mmol) was dissolved in anhydrous MeCN (20 mL), NIS (1.21 g, 5.39 mmol, 1.15 equiv.) was added in few portions and the reaction mixture was stirred for 5.5 h at rt. Then, solvent was evaporated and the residue was dissolved in DCM (30 mL), washed with 10% aq.  $\text{Na}_2\text{S}_2\text{O}_5$  (20 mL) and water (3×20 mL). The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Column chromatography (EtOAc/DCM 1:1) afforded 1.21 g, 76% of a colorless solid; mp 137.3–137.8 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.68–8.71 (m, 1H, CH), 7.91–7.97 (m, 1H, CH), 7.68–7.76 (m, 1H, CH), 7.20–7.26 (m, 1H, CH), 4.03 (s, 2H, H6), 2.72 (s, 2H, H4), 1.33 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  153.8 (C), 152.4 (C), 150.6



(C), 149.5 (CH), 136.3 (CH), 122.6 (CH), 122.0 (CH), 62.5 (C6), 50.0 (C3), 42.6 (C5), 39.3 (C4), 28.4 (C5a,b). FTIR (neat): 2949, 2937, 2924, 2874, 2865, 1587, 1564, 1528, 1497, 1465, 1444, 1433, 1406, 1390, 1371, 1349, 1320, 1274, 1259, 1178, 1147, 1107, 1087, 1008. Anal. Calcd. for  $C_{13}H_{14}N_3I$ : C, 46.03; H, 4.16; N, 12.39. Found: C, 45.93; H, 4.18; N, 12.23.

### 3-Bromo-5,5-dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole

**(6d).** **3e** (1.00 g, 4.40 mmol) was dissolved in anhydrous  $CHCl_3$  (20 mL), NBS (1.17 g, 6.60 mmol, 1.5 equiv.) was added in few portions and the reaction mixture was stirred for 0.75 h at rt. DCM (20 mL) was added and the mixture was washed with 10% aq.  $Na_2S_2O_5$  (10 mL) and water (3×20 mL). The collected organic phases were dried over  $MgSO_4$  and evaporated. Column chromatography (EtOAc/DCM 1:2) afforded 1.23 g, 91% of light yellow oil.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  7.74 (d,  $^3J = 7.8$ , 1H, CH), 7.59 (t,  $^3J = 7.7$ , 1H, CH), 7.07 (d,  $^3J = 7.5$ , 1H, CH), 3.97 (s, 2H, H6), 2.68 (s, 2H, H4), 2.63 (s, 3H,  $CH_3$ ), 1.28 (s, 6H, H5a,b).  $^{13}C$  { $^1H$ } NMR ( $CDCl_3$ ):  $\delta_C$  158.2 (C), 151.1 (C), 150.6 (C), 145.6 (C), 136.1 (CH), 121.9 (CH), 119.0 (CH), 86.1 (C3), 61.9 (C6), 42.5 (C5), 38.1 (C4), 27.9 (C5a,b), 24.5 (Ar- $CH_3$ ). FTIR (neat): 3056, 2959, 2926, 2872, 1715, 1590, 1577, 1544, 1490, 1464, 1440, 1428, 1404, 1389, 1371, 1341, 1322, 1292, 1264, 1189, 1113, 1088, 1034, 997. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{14}H_{16}N_3Br$ : 306.0600. Found: 306.0603.

### Pyridin-2-yl and 6-Methylpyridin-2-yl Substituted Products at C2: C-H Activation /

**Functionalization Products.** **3d** or **3e** (100 mg), relevant aryl bromide (1.2 equiv. for **7a,c,d,f,h-j** and **8a-c**, 1.5 equiv. for **8h**, 2.5 equiv. for **7g,m-o** and **8f,g,j**, 2.5 equiv. of 4-bromopyridine hydrochloride for **7l** and **8e**) or 4 equiv. of iodobenzene for **7q**, KOAc (1.2

equiv. for **7a,c,d,f,h-j** and **8a-c**, 3 equiv. for **7g,m-o** and **8f-h,j**, 4 equiv. for **7q**, 5 equiv. for **7l** and **8e**) and Pd(OAc)<sub>2</sub> (5 mol% for **7a,c,d,f,h-j** and **8a-c**, 10 mol% for **7l-o,q** and **8e,f,j**, 20 mol% for **7g** and **8g,h**) were mixed in anhydrous DMA (4 mL) and stirred at 150 °C under an argon atmosphere for 20 h (**7a,c,d,f,h-j,l,m** and **8a-c,e,f**), 24 h (**7g,n,o** and **8g,h**) 34 h (**8j**) or 100 h (**7q**). The conversion was monitored by TLC and <sup>1</sup>H NMR experiments. After consumption of the starting material, solvent was evaporated and the crude product was purified by column chromatography and/or by crystallization (MeCN).

**5,5-Dimethyl-3-(4-nitrophenyl)-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole**

**(7a)**. Column chromatography (MeOH/DCM 1:20) afforded 149 mg, 95% of yellow solid; mp 223.8–224.8 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 8.52–8.57 (m, 1H, CH), 8.12 (d, <sup>3</sup>J = 8.7, 2H, 2×CH), 7.65–7.73 (m, 1H, CH), 7.58–7.64 (m, 1H, CH), 7.40 (d, <sup>3</sup>J = 8.7, 2H, 2×CH), 7.19–7.25 (m, 1H, CH), 4.00 (s, 2H, H6), 2.86 (s, 2H, H4), 1.36 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ<sub>C</sub> 152.9 (C), 152.2 (C), 149.4 (CH), 145.9 (C), 145.7 (C), 141.0 (C), 136.7 (CH), 128.9 (2×CH), 123.6 (2×CH), 123.1 (CH), 122.9 (CH), 113.3 (C3), 61.4 (C6), 43.3 (C5), 39.5 (C4), 28.3 (C5a,b). FTIR (neat): 2960, 2930, 2891, 2872, 1596, 1587, 1552, 1507, 1496, 1443, 1416, 1402, 1342, 1326, 1274, 1253, 1176, 1126, 1108, 1094, 1084, 1045, 984. Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.49; H, 5.45; N, 16.64.

**4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)aniline (7b)**.

**7a** (100 mg, 0.299 mmol) was dissolved in anhydrous MeOH (4 mL) and 5% Pd/C (64 mg, 0.030 mmol, 10 mol%) was added. The reaction mixture was stirred at rt under a

hydrogen atmosphere (balloon) for 4 h. Pd/C was then filtered off, washed with MeOH (4×5 mL) and solvent was evaporated. Column chromatography (MeOH/DCM 1:22) afforded 82 mg, 90% of yellow solid; mp 229.3–229.8 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.61–8.64 (m, 1H, CH), 7.51–7.56 (m, 1H, CH), 7.39–7.42 (m, 1H, CH), 7.11–7.16 (m, 1H, CH), 7.03–7.06 (m, 2H, 2×CH), 6.60–6.64 (m, 2H, 2×CH), 3.98 (s, 2H, H6), 3.94 (bs, 2H,  $\text{NH}_2$ ), 2.78 (s, 2H, H4), 1.32 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  153.5 (C), 151.4 (C), 149.7 (CH), 144.1 (C), 143.9 (C), 135.9 (CH), 129.8 (2×CH), 123.9 (C), 123.1 (CH), 122.0 (CH), 115.2 (2×CH), 115.1 (C3), 61.3 (C6), 43.1 (C5), 39.1 (C4), 28.4 (C5a,b). FTIR (neat): 3449, 3393, 3321, 3207, 2957, 2927, 2869, 2847, 1617, 1587, 1557, 1511, 1495, 1466, 1443, 1410, 1370, 1317, 1288, 1271, 1179, 1141, 1124, 1089, 1046, 993. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{19}\text{H}_{20}\text{N}_4$ : 305.1761. Found: 305.1763.

**4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)benzonitrile (7c).** Column chromatography (EtOAc) afforded 127 mg, 87% of an off-white solid; mp 225.4–225.6 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.53–8.58 (m, 1H, CH), 7.63–7.70 (m, 1H, CH), 7.56–7.61 (m, 1H, CH), 7.54 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.37 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.18–7.24 (m, 1H, CH), 4.00 (s, 2H, H6), 2.85 (s, 2H, H4), 1.36 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  152.9 (C), 152.0 (C), 149.4 (CH), 145.4 (C), 138.8 (C), 136.4 (CH), 131.9 (2×CH), 128.9 (2×CH), 122.9 (CH), 122.6 (CH), 119.2 (C), 113.5 (C3), 109.2 (CN), 61.3 (C6), 43.2 (C5), 39.3 (C4), 28.2 (C5a,b). FTIR (neat): 2962, 2885, 2872, 2223, 1605, 1588, 1559, 1544, 1489, 1465, 1448, 1415, 1400, 1393, 1372, 1318, 1299, 1281, 1257, 1178, 1140, 1127, 1099, 1088, 1046, 995. Anal. Calcd. for  $\text{C}_{20}\text{H}_{18}\text{N}_4$ : C, 76.41; H, 5.77; N, 17.82. Found: C, 76.24; H, 5.88; N, 17.63.

**4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)benzaldehyde (7d).** Column chromatography (EtOAc) afforded 135 mg, 91% of a colorless solid; mp 197.7–198.6 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  9.97 (s, 1H, HC=O), 8.56–8.61 (m, 1H, CH), 7.79 (d,  $^3J = 8.3$ , 2H, 2×CH), 7.61–7.69 (m, 1H, CH), 7.53–7.58 (m, 1H, CH), 7.42 (d,  $^3J = 8.3$ , 2H, 2×CH), 7.18–7.24 (m, 1H, CH), 4.01 (s, 2H, H6), 2.88 (s, 2H, H4), 1.37 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  191.9 (HC=O), 153.1 (C), 152.3 (C), 149.7 (CH), 145.5 (C), 140.5 (C), 136.4 (CH), 134.2 (C), 129.9 (2×CH), 128.9 (2×CH), 123.2 (CH), 122.7 (CH), 114.1 (C3), 61.4 (C6), 43.3 (C5), 39.5 (C4), 28.4 (C5a,b). FTIR (neat): 2959, 2929, 2879, 2848, 1687, 1666, 1601, 1588, 1551, 1488, 1463, 1446, 1407, 1392, 1368, 1304, 1276, 1214, 1183, 1166, 1125, 1098, 1086, 995. Anal. Calcd. for  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}$ : C, 75.69; H, 6.03; N, 13.24. Found: C, 75.37; H, 5.98; N, 13.08.

**(4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)phenyl)**

**methanol (7e).** **7d** (100 mg, 0.315 mmol) was dissolved in anhydrous MeOH (7 mL),  $\text{NaBH}_4$  (14.3 mg, 0.378 mmol, 1.2 equiv.) was added and the reaction mixture became clear in 5 min. After 30 min, the reaction was quenched with water (10 mL) and methanol was evaporated. The product was extracted with DCM (3×10 mL) and the organic phase was dried over  $\text{Na}_2\text{SO}_4$  and evaporated. The final product was crystallized from MeCN to yield 86 mg, 85% of a colorless solid; mp 179.1–180.0 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.54–8.60 (m, 1H, CH), 7.51–7.59 (m, 1H, CH), 7.40–7.46 (m, 1H, CH), 7.18–7.28 (m, 4H, 4×CH), 7.11–7.17 (m, 1H, CH), 4.61 (s, 2H,  $\text{CH}_2\text{OH}$ ), 3.97 (s, 2H, H6), 2.96 (bs, 1H, OH), 2.79 (s, 2H, H4), 1.31 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  153.2 (C), 151.6 (C), 149.6 (CH), 144.7 (C), 139.2 (C), 136.1 (CH), 132.8 (C), 128.7 (2×CH), 127.1 (2×CH), 123.1

(CH), 122.2 (CH), 114.8 (C3), 64.8 (CH<sub>2</sub>OH), 61.3 (C6), 43.1 (C5), 39.2 (C4), 28.3 (C5a,b).

FTIR (neat): 3357, 2952, 2930, 2888, 2865, 1588, 1552, 1491, 1465, 1447, 1415, 1401, 1387, 1367, 1327, 1299, 1257, 1209, 1182, 1140, 1110, 1088, 1046, 1019. HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> Calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O: 320.1757. Found: 320.1763.

**3-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)benzaldehyde (7f).** Column chromatography (EtOAc) afforded 125 mg, 84% of a colorless solid; mp 140.9–141.1 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 9.94 (s, 1H, HC=O), 8.51–8.58 (m, 1H, CH), 7.80–7.85 (m, 1H, CH), 7.68–7.74 (m, 1H, CH), 7.51–7.66 (m, 3H, 3×CH), 7.38–7.46 (m, 1H, CH), 7.14–7.20 (m, 1H, CH), 4.00 (s, 2H, H6), 2.86 (s, 2H, H4), 1.34 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ<sub>C</sub> 192.1 (HC=O), 152.9 (C), 151.5 (C), 149.2 (CH), 144.9 (C), 136.4 (C), 136.1 (CH), 134.7 (C), 134.6 (CH), 129.5 (CH), 128.7 (CH), 127.2 (CH), 122.6 (CH), 122.3 (CH), 113.6 (C3), 61.2 (C6), 43.0 (C5), 39.0 (C4), 28.1 (C5a,b). FTIR (neat): 2954, 2938, 2879, 2826, 2801, 2774, 2731, 1693, 1606, 1586, 1566, 1548, 1490, 1467, 1450, 1406, 1377, 1369, 1322, 1288, 1190, 1167, 1141, 1124, 1091, 1079, 1018, 998. Anal. Calcd. for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.68; H, 6.03; N, 13.12.

**2-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)benzaldehyde (7g).** Column chromatography (1<sup>st</sup> EtOAc, 2<sup>nd</sup> EtOAc/DCM 1:1) afforded 83 mg, 56% of light yellow solid; mp 81.8–83.0 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 10.01 (s, 1H, HC=O), 8.38–8.45 (m, 1H, CH), 7.95–8.01 (m, 1H, CH), 7.49–7.60 (m, 3H, 3×CH), 7.37–7.47 (m, 1H, CH), 7.25–7.33 (m, 1H, CH), 7.05–7.13 (m, 1H, CH), 4.05 (s, 2H, H6), 2.70 (s, 2H, H4), 1.35 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 191.7 (HC=O), 152.4 (C), 152.3 (C), 149.2 (CH), 146.4 (C), 137.6 (C), 136.4 (CH), 134.5 (C), 133.4 (CH), 131.5 (CH),

127.4 (CH), 127.2 (CH), 122.4 (CH), 121.8 (CH), 111.1 (C3), 61.6 (C6), 43.3 (C5), 38.6 (C4), 28.3 (C5a,b). FTIR (neat): 2960, 2926, 2870, 2854, 2754, 1695, 1657, 1589, 1549, 1497, 1486, 1464, 1449, 1410, 1391, 1367, 1323, 1268, 1246, 1198, 1181, 1152, 1131, 1120, 996. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{20}H_{19}N_3O$ : 318.1601. Found: 318.1602.

**1-(4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)phenyl)ethanone (7h).** Column chromatography (EtOAc) afforded 124 mg, 80% of light yellow solid; mp 154.9–155.2 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.54–8.63 (m, 1H, CH), 7.87 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.58–7.66 (m, 1H, CH), 7.50–7.57 (m, 1H, CH), 7.36 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.14–7.22 (m, 1H, CH), 4.00 (s, 2H, H6), 2.85 (s, 2H, H4), 2.55 (s, 3H,  $H_3C-C=O$ ), 1.34 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  197.3 (C=O), 152.9 (C), 151.8 (C), 149.3 (CH), 145.0 (C), 138.7 (C), 136.0 (CH), 134.5 (C), 128.2 (2×2CH), 122.8 (CH), 122.2 (CH), 113.8 (C3), 61.1 (C6), 42.9 (C5), 39.1 (C4), 28.0 (C5a,b), 26.3 ( $H_3C-C=O$ ). FTIR (neat): 2964, 2947, 2875, 1675, 1601, 1562, 1542, 1491, 1476, 1431, 1419, 1399, 1356, 1288, 1269, 1182, 1142, 1126, 1092, 1043, 985. Anal. Calcd. for  $C_{21}H_{21}N_3O$ : C, 76.11; H, 6.39; N, 12.68. Found: C, 75.80; H, 6.56; N, 12.49.

**1-(4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)phenyl)octan-1-one (7i).** Column chromatography (EtOAc) afforded 174 mg, 89% of light yellow solid; mp 78.4–79.4 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.58–8.62 (m, 1H, CH), 7.88 (d,  $^3J = 8.3$ , 2H, 2×CH), 7.58–7.66 (m, 1H, CH), 7.49–7.55 (m, 1H, CH), 7.35 (d,  $^3J = 8.3$ , 2H, 2×CH), 7.15–7.21 (m, 1H, CH), 4.00 (s, 2H, H6), 2.93 (t,  $^3J = 7.4$ , 2H,  $CH_2$ ), 2.86 (s, 2H, H4), 1.67–1.80 and 1.23–1.44 (m, 10H), 1.35 (s, 6H, H5a,b), 0.88 (t,  $^3J = 6.8$ , 3H,  $CH_3$ ).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  199.9 (C=O), 153.1 (C), 152.0 (C), 149.5 (CH), 145.1 (C), 138.6 (C), 136.2

(CH), 134.6 (C), 128.4 (2×CH), 128.1 (2×CH), 123.0 (CH), 122.4 (CH), 114.1 (C3), 61.3 (C6), 43.1 (C5), 39.3 (C4), 38.5 (CH<sub>2</sub>), 31.7 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 28.2 (C5a,b), 24.5 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.1 (CH<sub>3</sub>). FTIR (neat): 2938, 2917, 2868, 2849, 1680, 1605, 1588, 1550, 1492, 1461, 1452, 1432, 1418, 1401, 1370, 1317, 1303, 1273, 1233, 1192, 1182, 1146, 1124, 1094, 1045, 993. Anal. Calcd. for C<sub>27</sub>H<sub>33</sub>N<sub>3</sub>O: C, 78.03; H, 8.00; N, 10.11. Found: C, 77.79; H, 8.07; N, 9.97.

**Ethyl-4-(5,5-dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)benzoate (7j).** Column chromatography (EtOAc) afforded 136 mg, 80% of an off-white solid; mp 143.1–144.6 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 8.58–8.62 (m, 1H, CH), 7.95 (d, <sup>3</sup>J = 8.4, 2H, 2×CH), 7.57–7.64 (m, 1H, CH), 7.43–7.47 (m, 1H, CH), 7.30 (d, <sup>3</sup>J = 8.4, 2H, 2×CH), 7.16–7.21 (m, 1H, CH), 4.35 (q, <sup>3</sup>J = 7.2, 2H, CH<sub>2</sub>CH<sub>3</sub>), 4.00 (s, 2H, H6), 2.84 (s, 2H, H4), 1.37 (t, <sup>3</sup>J = 7.2, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.34 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ<sub>C</sub> 166.6 (C=O), 153.0 (C), 152.0 (C), 149.7 (CH), 145.2 (C), 138.5 (C), 136.3 (CH), 129.7 (2×CH), 128.3 (2×CH), 128.0 (C), 123.1 (CH), 122.5 (CH), 114.1 (C3), 61.3 (C6), 60.9 (CH<sub>2</sub>CH<sub>3</sub>), 43.2 (C5), 39.3 (C4), 28.4 (C5a,b), 14.5 (CH<sub>2</sub>CH<sub>3</sub>). FTIR (neat): 3042, 2960, 2933, 2905, 2873, 1712, 1610, 1589, 1565, 1554, 1487, 1465, 1446, 1416, 1402, 1390, 1368, 1323, 1310, 1289, 1273, 1179, 1109, 1046, 1023, 995, 984. HRMS (ESI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>22</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>: 362.1863. Found: 362.1864.

**4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)benzoic acid (7k).** **7j** (100 mg, 0.277 mmol) was dissolved in the mixture of EtOH/THF 1:1 (3+3 mL) and 1 M NaOH was added (1.4 mL, 1.38 mmol, 5 equiv.). The colorless mixture was stirred at rt for 16 h, solvents were evaporated and water was added (1 mL). The crude

product was obtained after neutralization with 1M HCl and its filtration. The amorphous solid was washed with DCM (5 mL), dried under reduced pressure and crystallized (MeOH) to yield 74 mg, 80% of a colorless solid; mp 301.2–302.1 °C.  $^1\text{H}$  NMR (MeOD- $d_4$ ):  $\delta_{\text{H}}$  12.80 (bs, 1H, OH), 8.42–8.48 (m, 1H, CH), 7.78–7.86 (m, 3H, 3 $\times$ CH) 7.69–7.73 (m, 1H, CH), 7.35 (d,  $^3J$  = 8.3, 2H, 2 $\times$ CH), 7.30–7.34 (m, 1H, CH), 3.98 (s, 2H, H6), 2.88 (s, 2H, H4), 1.29 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (MeOD- $d_4$ ):  $\delta_{\text{C}}$  167.2 (C=O), 153.1 (C), 150.8 (C), 148.7 (CH), 145.5 (C), 138.4 (C), 136.8 (CH), 129.0 (2 $\times$ CH), 128.2 (2 $\times$ CH), 127.8 (C), 122.7 (CH), 122.4 (CH), 113.5 (C3), 60.5 (C6), 42.8 (C5), 38.5 (C4), 27.7 (C5a,b). FTIR (KBr): 3436, 3057, 2960, 2874, 1699, 1611, 1590, 1566, 1553, 1490, 1465, 1448, 1417, 1403, 1372, 1311, 1241, 1179, 1115, 1100, 1048, 998. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{20}\text{H}_{20}\text{N}_3\text{O}_2$ : 334.1550. Found: 334.1551.

**5,5-Dimethyl-2-(pyridin-2-yl)-3-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole**

**(7I).** Column chromatography (MeOH/EtOAc 1:4) afforded 114 mg, 84% of a colorless solid; mp 193.2–193.3 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.56–8.62 (m, 1H, CH), 8.48 (d,  $^3J$  = 6.2, 2H, 2 $\times$ CH), 7.63–7.72 (m, 1H, CH), 7.55–7.62 (m, 1H, CH), 7.19–7.26 (m, 1H, CH), 7.18 (d,  $^3J$  = 6.2, 2H, 2 $\times$ CH), 4.00 (s, 2H, H6), 2.88 (s, 2H, H4), 1.36 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  152.9 (C), 152.4 (C), 149.6 (2 $\times$ CH), 149.5 (CH), 145.6 (C), 141.7 (C), 136.4 (CH), 123.0 (CH), 123.0 (2 $\times$ CH), 122.7 (CH), 112.4 (C3), 61.3 (C6), 43.2 (C5), 39.5 (C4), 28.3 (C5a,b). FTIR (neat): 2960, 2928, 2887, 2868, 1601, 1589, 1558, 1540, 1491, 1444, 1408, 1374, 1320, 1311, 1279, 1261, 1219, 1181, 1146, 1106, 1089, 1049, 1004, 987. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{18}\text{H}_{18}\text{N}_4$ : 291.1604. Found: 291.1609.



**5,5-Dimethyl-3-(2-methylpyridin-4-yl)-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-**

**b]pyrazole (7m).** Column chromatography (MeOH/EtOAc 1:5) afforded 141 mg, 99% of an off-white solid; mp 144.7–146.0 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.56–8.60 (m, 1H, CH), 8.32–8.35 (m, 1H, CH), 7.62–7.68 (m, 1H, CH), 7.50–7.54 (m, 1H, CH), 7.18–7.23 (m, 1H, CH), 7.02 (s, 1H, CH), 6.91–6.96 (m, 1H, CH), 3.98 (s, 2H, H6), 2.85 (s, 2H, H4), 2.47 (s, 3H,  $\text{CH}_3$ ), 1.33 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  158.1 (C), 152.8 (C), 152.3 (C), 149.6 (CH), 148.8 (CH), 145.6 (C), 142.0 (C), 136.4 (CH), 123.1 (CH), 122.7 (CH), 122.4 (CH), 120.3 (CH), 112.5 (C), 61.3 (C6), 43.3 (C5), 39.4 (C4), 28.3 (C5a,b), 24.4 ( $\text{CH}_3$ ). FTIR (neat): 3048, 3008, 2958, 2930, 2872, 1606, 1589, 1562, 1543, 1500, 1489, 1467, 1446, 1415, 1391, 1370, 1322, 1315, 1289, 1275, 1266, 1213, 1181, 1149, 1138, 1123, 1091, 1046, 1029, 997, 990. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{19}\text{H}_{21}\text{N}_4$ : 305.1761. Found: 305.1760.

**4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)quinoline**

**(7n).** Column chromatography (MeOH/EtOAc 1:6) afforded 145 mg, 91% of an off-white solid; mp 217.2–217.3 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.87 (d,  $^3J = 4.5$ , 1H, CH), 8.40–8.45 (m, 1H, CH), 8.14 (d,  $^3J = 8.4$ , 1H, CH), 7.77 (d,  $^3J = 8.4$ , 1H, CH), 7.62–7.71 (m, 1H, CH), 7.33–7.46 (m, 2H, 2 $\times$ CH), 7.29 (d,  $^3J = 4.5$ , 1H, CH), 7.19–7.26 (m, 1H, CH), 7.00–7.07 (m, 1H, CH), 4.10 (s, 2H, H6), 2.65 (s, 2H, H4), 1.36 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  152.6 (C), 152.1 (C), 149.8 (CH), 149.4 (CH), 148.5 (C), 146.1 (C), 141.1 (C), 135.9 (CH), 129.6 (CH), 129.1 (CH), 127.2 (C), 126.1 (CH), 125.9 (CH), 122.4 (CH), 122.0 (CH), 121.8 (CH), 110.6 (C3), 61.4 (C6), 43.1 (C5), 38.7 (C4), 28.0 (C5a,b). FTIR (neat): 3030, 2957, 2930, 2889, 2869, 1584, 1565, 1502, 1489, 1447, 1416, 1389, 1370, 1316, 1281, 1271, 1180, 1170,

1148, 1125, 1081, 1048, 1018, 991. Anal. Calcd. for C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>: C, 77.62; H, 5.92; N, 16.46.

Found: C, 77.37; H, 5.80; N, 16.27.

**4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)quinoline-6-carbonitrile (7o).** Column chromatography (MeOH/EtOAc 1:5) afforded 103 mg, 60% of light yellow solid; mp 185.7–187.1 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> 8.96 (d, <sup>3</sup>*J* = 4.4, 1H, CH), 8.15–8.22 (m, 2H, 2×CH), 8.12 (s, 1H, CH), 7.75 (d, <sup>3</sup>*J* = 8.8, 1H, CH), 7.54–7.65 (m, 2H, 2×CH), 7.40 (d, <sup>3</sup>*J* = 4.4, 1H, CH), 6.99–7.11 (m, 1H, CH), 4.10 (s, 2H, H<sub>6</sub>), 2.66 (s, 2H, H<sub>4</sub>), 1.37 (s, 6H, H<sub>5a,b</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ<sub>C</sub> 152.9 (C), 152.8 (CH), 152.0 (C), 149.5 (C), 149.3 (CH), 146.6 (C), 142.6 (C), 136.5 (CH), 133.2 (CH), 131.2 (CH), 129.7 (CH), 127.1 (C), 123.7 (CH), 122.5 (CH), 121.8 (CH), 118.8 (C), 109.7 (CN), 109.7 (C<sub>3</sub>), 61.6 (C<sub>6</sub>), 43.5 (C<sub>5</sub>), 38.9 (C<sub>4</sub>), 28.2 (C<sub>5a,b</sub>). FTIR (neat): 3049, 3016, 2959, 2928, 2872, 2854, 2227, 1729, 1646, 1588, 1566, 1497, 1464, 1451, 1428, 1412, 1390, 1372, 1357, 1323, 1308, 1274, 1254, 1211, 1180, 1145, 1115, 1091, 1045, 992. HRMS (ESI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>23</sub>H<sub>20</sub>N<sub>5</sub>: 366.1713. Found: 366.1714.

**4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)quinoline-6-carboxamide (7p).** **7o** (50 mg, 0.137 mmol) was dissolved in DMSO (0.5 mL), K<sub>2</sub>CO<sub>3</sub> (4.2 mg, 0.030 mmol, 0.2 equiv.) was added and finally 30% aq. H<sub>2</sub>O<sub>2</sub> (18 μL, 0.178 mmol, 1.3 equiv.) in H<sub>2</sub>O (25 μL) was added dropwise (gently exothermic). The solution was stirred for 4 h at rt and Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (13 mg) in H<sub>2</sub>O (0.4 mL) was added. Solvents were evaporated and the crude product was purified by preparative HPLC (MeCN/H<sub>2</sub>O/CF<sub>3</sub>COOH) and lyophilized to get 62 mg, 90% of light yellow solid as trifluoroacetate salt; mp 90.0–91.6 °C. <sup>1</sup>H NMR (CD<sub>3</sub>CN): δ<sub>H</sub> 9.07 (d, <sup>3</sup>*J* = 5.5, 1H, CH), 8.59 (d, <sup>3</sup>*J* = 5.7, 1H, CH), 8.49 (s, 1H,

CH), 8.42–8.46 (m, 2H, 2×CH), 8.16 (t,  $^3J = 7.9$ , 1H, CH), 7.82 (d,  $^3J = 5.5$ , 1H, CH), 7.74 (t,  $^3J = 6.7$ , 1H, CH), 7.62 (d,  $^3J = 8.1$ , 1H, CH), 7.32 (bs, 1H, NH<sub>2</sub>), 6.42 (bs, 1H, NH<sub>2</sub>), 4.15 (s, 2H, H<sub>6</sub>), 2.76 (s, 2H, H<sub>4</sub>), 1.34 (s, 6H, H<sub>5a,b</sub>).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (CD<sub>3</sub>CN):  $\delta_{\text{C}}$  167.7 (O=C-NH<sub>2</sub>), 160.9 (q,  $^2J_{\text{C,F}} = 37.1$ , CF<sub>3</sub>C=O), 150.9 (C), 150.8 (C), 146.7 (CH), 146.5 (CH), 146.5 (C), 146.1 (C), 144.1 (CH), 142.2 (C), 135.1 (C), 133.5 (CH), 127.8 (C), 127.7 (CH), 126.5 (CH), 126.4 (CH), 124.6 (CH), 123.8 (CH), 117.0 (q,  $^1J_{\text{C,F}} = 288.8$ , CF<sub>3</sub>), 111.5 (C<sub>3</sub>), 62.6 (C<sub>6</sub>), 44.5 (C<sub>5</sub>), 39.5 (C<sub>4</sub>), 27.7 (C<sub>5a,b</sub>). FTIR (KBr): 3411, 3195, 3102, 2965, 2936, 2878, 1774, 1678, 1625, 1608, 1544, 1488, 1466, 1452, 1417, 1379, 1321, 1280, 1269, 1200, 1183, 1139, 1064, 964. HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> Calcd. for C<sub>23</sub>H<sub>22</sub>N<sub>5</sub>O: 384.1819. Found: 384.1821.

**5,5-Dimethyl-3-phenyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (7q).**

Column chromatography (1<sup>st</sup> EtOAc, 2<sup>nd</sup> MeOH/DCM 1:25) afforded 58 mg, 47% of a colorless solid; mp 145.9–147.1 °C.  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta_{\text{H}}$  8.60–8.64 (m, 1H, CH), 7.51–7.58 (m, 1H, CH), 7.39–7.43 (m, 1H, CH), 7.17–7.30 (m, 5H, 5×CH), 7.11–7.16 (m, 1H, CH), 3.99 (s, 2H, H<sub>6</sub>), 2.81 (s, 2H, H<sub>4</sub>), 1.32 (s, 6H, H<sub>5a,b</sub>).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (CDCl<sub>3</sub>):  $\delta_{\text{C}}$  153.3 (C), 151.6 (C), 149.7 (CH), 144.6 (C), 135.9 (CH), 133.7 (C), 128.7 (2×CH), 128.3 (2×CH), 126.2 (CH), 123.1 (CH), 122.1 (CH), 115.0 (C<sub>3</sub>), 61.3 (C<sub>6</sub>), 43.1 (C<sub>5</sub>), 39.1 (C<sub>4</sub>), 28.3 (C<sub>5a,b</sub>). FTIR (neat): 3055, 2954, 2926, 2879, 1602, 1586, 1567, 1551, 1501, 1485, 1464, 1446, 1409, 1386, 1367, 1327, 1304, 1277, 1258, 1178, 1141, 1124, 1101, 1086, 1073, 1047, 993. HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> Calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>: 290.1652. Found: 290.1661.

**4-(5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)benzonitrile (8a).** Column chromatography (EtOAc) afforded 120 mg, 83% of a colorless solid; mp 195.3–196.1 °C.  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta_{\text{H}}$  7.49–7.57 (m, 3H, 3×CH), 7.35–

7.41 (m, 2H, 2×CH), 7.29 (d,  $^3J = 7.6$ , 1H, CH), 7.08 (d,  $^3J = 7.6$ , 1H, CH), 4.01 (s, 2H, H6), 2.85 (s, 2H, H4), 2.51 (s, 3H, CH<sub>3</sub>), 1.35 (s, 6H, H5a,b).  $^{13}\text{C} \{^1\text{H}\}$  NMR (CDCl<sub>3</sub>):  $\delta_{\text{C}}$  158.5 (C), 152.3 (C), 152.1 (C), 145.2 (C), 139.0 (C), 136.6 (CH), 131.9 (2×CH), 129.0 (2×CH), 122.2 (CH), 120.1 (CH), 119.3 (C), 113.5 (C3), 109.2 (CN), 61.4 (C6), 43.2 (C5), 39.4 (C4), 28.3 (C5a,b), 24.5 (CH<sub>3</sub>). FTIR (neat): 2962, 2926, 2885, 2870, 2851, 2224, 1606, 1588, 1572, 1560, 1541, 1482, 1440, 1425, 1397, 1381, 1369, 1353, 1325, 1304, 1271, 1246, 1178, 1158, 1127, 1088, 1006, 994. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>: 329.1761. Found: 329.1765.

**4-(5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)benzaldehyde (8b).** Column chromatography (EtOAc) afforded 130 mg, 89% of light yellow solid; mp 186.8–187.7 °C.  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta_{\text{H}}$  9.97 (s, 1H, HC=O), 7.76–7.80 (m, 2H, 2×CH), 7.51 (t,  $^3J = 7.7$ , 1H, CH), 7.39–7.46 (m, 2H, 2×CH), 7.25 (d,  $^3J = 7.7$ , 1H, CH), 7.08 (d,  $^3J = 7.7$ , 1H, CH), 4.02 (s, 2H, H6), 2.88 (s, 2H, H4), 2.54 (s, 3H, CH<sub>3</sub>), 1.36 (s, 6H, H5a,b).  $^{13}\text{C} \{^1\text{H}\}$  NMR (CDCl<sub>3</sub>):  $\delta_{\text{C}}$  191.9 (HC=O), 158.6 (C), 152.6 (C), 152.3 (C), 145.3 (C), 140.6 (C), 136.6 (CH), 134.2 (C), 129.8 (2×CH), 129.0 (2×CH), 122.3 (CH), 120.5 (CH), 114.0 (C3), 61.5 (C6), 43.3 (C5), 39.6 (C4), 28.5 (C5a,b), 24.7 (CH<sub>3</sub>). FTIR (neat): 2958, 2926, 2872, 2846, 1691, 1602, 1589, 1568, 1547, 1488, 1460, 1440, 1426, 1389, 1367, 1354, 1325, 1303, 1270, 1216, 1183, 1167, 1158, 1126, 1088, 1006, 994. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O: 332.1757. Found: 332.1762.

**Ethyl-4-(5,5-dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)benzoate (8c).** Column chromatography (EtOAc) afforded 114 mg, 69% of a colorless solid; mp 116.3–117.7 °C.  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta_{\text{H}}$  7.94 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.46 (t,  $^3J = 7.7$ ,

1H, CH), 7.30 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.15 (d,  $^3J = 7.7$ , 1H, CH), 7.06 (d,  $^3J = 7.7$ , 1H, CH), 4.35 (q,  $^3J = 7.1$ , 2H, CH<sub>2</sub>CH<sub>3</sub>), 4.00 (s, 2H, H<sub>6</sub>), 2.84 (s, 2H, H<sub>4</sub>), 2.56 (s, 3H, CH<sub>3</sub>), 1.37 (t,  $^3J = 7.1$ , 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.33 (s, 6H, H<sub>5a,b</sub>).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (CDCl<sub>3</sub>):  $\delta_{\text{C}}$  166.7 (C=O), 158.7 (C), 152.2 (C), 145.0 (C), 138.6 (C), 136.5 (CH), 129.6 (2×CH), 128.3 (2×CH), 127.9 (C), 122.1 (CH), 120.5 (CH), 114.0 (C<sub>3</sub>), 61.3 (C<sub>6</sub>), 60.9 (CH<sub>2</sub>CH<sub>3</sub>), 43.2 (C<sub>5</sub>), 39.3 (C<sub>4</sub>), 28.4 (C<sub>5a,b</sub>), 24.7 (CH<sub>3</sub>), 14.5 (CH<sub>2</sub>CH<sub>3</sub>). FTIR (neat): 3057, 2960, 2931, 2906, 2873, 1712, 1610, 1590, 1578, 1554, 1491, 1481, 1465, 1431, 1398, 1389, 1367, 1324, 1309, 1273, 1179, 1158, 1103, 1025, 1007, 994. HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> Calcd. for C<sub>23</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>: 376.2020. Found: 376.2021.

**4-(5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)benzoic acid (8d).** **8c** (100 mg, 0.266 mmol) was dissolved in a mixture of EtOH/THF 1:1 (3+3 mL) and 1M NaOH was added (1.3 mL, 1.33 mmol, 5 equiv.). The colorless mixture was stirred at rt for 18 h. Solvents were evaporated and water (1 mL) was added. The crude product was obtained after neutralization with 1M HCl and by following filtration. The amorphous solid was washed with DCM (5 mL), dried under reduced pressure and crystallized from MeOH to get 83 mg, 90% of a colorless solid; mp 318.5–320.0 °C.  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  12.78 (bs, 1H, OH), 7.83 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.68 (t,  $^3J = 7.7$ , 1H, CH), 7.45 (d,  $^3J = 7.7$ , 1H, CH), 7.42 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.17 (d,  $^3J = 7.7$ , 1H, CH), 3.97 (s, 2H, H<sub>6</sub>), 2.88 (s, 2H, H<sub>4</sub>), 2.33 (s, 3H, CH<sub>3</sub>), 1.29 (s, 6H, H<sub>5a,b</sub>).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  167.3 (C=O), 157.0 (C), 152.4 (C), 150.9 (C), 145.3 (C), 138.4 (C), 136.8 (CH), 128.8 (2×CH), 128.3 (2×CH), 127.7 (C), 121.8 (CH), 119.4 (CH), 113.4 (C<sub>3</sub>), 60.5 (C<sub>6</sub>), 42.8 (C<sub>5</sub>), 38.6 (C<sub>4</sub>), 27.7 (C<sub>5a,b</sub>), 23.8 (CH<sub>3</sub>). FTIR (KBr): 3436, 3069, 2960,

1711, 1612, 1591, 1578, 1552, 1431, 1373, 1324, 1310, 1241, 1179, 1113, 1110, 1012,

995. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{21}H_{22}N_3O_2$ : 348.1707. Found: 348.1707.

**5,5-Dimethyl-2-(6-methylpyridin-2-yl)-3-(pyridine-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-**

**b]pyrazole (8e).** Column chromatography (MeOH/EtOAc 1:5) afforded 96 mg, 71% of a

colorless solid; mp 156.1–156.8 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.47 (d,  $^3J = 5.9$ , 2H, 2×CH), 7.55

(t,  $^3J = 7.7$ , 1H, CH), 7.32 (d,  $^3J = 7.7$ , 1H, CH), 7.22 (d,  $^3J = 5.9$ , 2H, 2×CH), 7.10 (d,  $^3J = 7.7$ ,

1H, CH), 4.01 (s, 2H, H6), 2.89 (s, 2H, H4), 2.53 (s, 3H,  $CH_3$ ), 1.36 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$

NMR ( $CDCl_3$ ):  $\delta_C$  158.5 (C), 152.7 (C), 152.1 (C), 148.9 (2×CH), 145.6 (C), 142.5 (C), 136.7

(CH), 123.1 (2×CH), 122.4 (CH), 120.3 (CH), 112.3 (C3), 61.3 (C6), 43.2 (C5), 39.6 (C4),

28.4 (C5a,b), 24.5 ( $CH_3$ ). FTIR (neat): 2952, 2921, 2852, 1600, 1584, 1572, 1539, 1467,

1427, 1401, 1388, 1372, 1350, 1314, 1291, 1266, 1218, 1179, 1149, 1138, 1082, 991.

HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{19}H_{20}N_4$ : 305.1761. Found: 305.1767.

**5,5-Dimethyl-2-(6-methylpyridin-2-yl)-3-(2-methylpyridine-4-yl)-5,6-dihydro-4H-**

**pyrrolo[1,2-b]pyrazole (8f).** Column chromatography (MeOH/EtOAc 1:5) afforded 114

mg, 81% of a colorless solid; mp 95.3–96.9 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.34 (d,  $^3J = 5.2$ , 1H,

CH), 7.52 (t,  $^3J = 7.7$ , 1H, CH), 7.26 (t,  $^3J = 7.7$ , 1H, CH), 7.06–7.12 (m, 2H, 2×CH), 6.96 (d,

$^3J = 5.2$ , 1H, CH), 4.00 (s, 2H, H6), 2.87 (s, 2H, H4), 2.55 (s, 3H,  $CH_3$ ), 2.49 (s, 3H,  $CH_3$ ),

1.34 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  158.5 (C), 158.0 (C), 152.5 (C), 152.0 (C),

148.8 (CH), 145.3 (C), 142.0 (C), 136.5 (CH), 122.4 (CH), 122.2 (CH), 120.3 (CH), 120.2

(CH), 112.4 (C3), 61.2 (C6), 43.2 (C5), 39.4 (C4), 28.3 (C5a,b), 24.6 ( $CH_3$ ), 24.5 ( $CH_3$ ). FTIR

(neat): 2966, 2886, 2874, 2855, 1608, 1594, 1578, 1545, 1494, 1478, 1465, 1437, 1390,

1372, 1360, 1324, 1310, 1293, 1246, 1182, 1160, 1142, 1090, 1000. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{20}H_{23}N_4$ : 319.1917. Found: 319.1919.

**4-(5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)quinoline (8g).** Column chromatography (MeOH/EtOAc 1:10) afforded 100 mg, 64% of a colorless solid; mp 182.9–184.0 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.81 (d,  $^3J = 4.4$ , 1H, CH), 8.09 (d,  $^3J = 8.1$ , 1H, CH), 7.74 (d,  $^3J = 9.2$ , 1H, CH), 7.62 (ddd,  $^3J = 8.4$ , 6.8, 1.5, 1H, CH), 7.33 (ddd,  $^3J = 8.4$ , 6.8, 1.5, 1H, CH), 7.25 (d,  $^3J = 4.4$ , 1H, CH), 7.22 (t,  $^3J = 7.7$ , 1H, CH), 6.90 (d,  $^3J = 7.7$ , 1H, CH), 6.86 (d,  $^3J = 7.7$ , 1H, CH), 4.06 (s, 2H, H6), 2.61 (s, 2H, H4), 2.31 (s, 3H, CH<sub>3</sub>), 1.30 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  158.4 (C), 152.9 (C), 151.3 (C), 149.9 (CH), 148.6 (C), 146.0 (C), 141.4 (C), 136.2 (CH), 129.7 (CH), 129.2 (CH), 127.4 (C), 126.2 (CH), 126.2 (CH), 122.5 (CH), 121.7 (CH), 119.2 (CH), 110.7 (C3), 61.5 (C6), 43.3 (C5), 38.8 (C4), 28.2 (C5a,b), 24.4 (CH<sub>3</sub>). FTIR (KBr): 3057, 3038, 2957, 2928, 2873, 1628, 1587, 1578, 1567, 1504, 1492, 1483, 1465, 1433, 1408, 1388, 1371, 1353, 1327, 1310, 1283, 1243, 1185, 1169, 1156, 1141, 1126, 1085, 1052, 1034, 1018, 986. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{23}H_{23}N_4$ : 355.1917. Found: 355.1919.

**4-(5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)quinoline-6-carbonitrile (8h).** Column chromatography (MeOH/EtOAc 1:6) afforded 145 mg, 87% of a colorless solid; mp 189.7–191.0 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.95 (d,  $^3J = 4.5$ , 1H, CH), 8.15 (d,  $^3J = 8.8$ , 1H, CH), 8.13 (s, 1H, CH), 7.73 (d,  $^3J = 8.8$ , 1H, CH), 7.37–7.42 (m, 2H, 2×CH), 7.29 (d,  $^3J = 7.6$ , 1H, CH), 6.87 (d,  $^3J = 7.6$ , 1H, CH), 4.09 (s, 2H, H6), 2.67 (s, 2H, H4), 2.03 (s, 3H, CH<sub>3</sub>), 1.35 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  158.0 (C), 153.0 (C), 152.7 (CH), 151.1 (C), 149.4 (C), 146.3 (C), 142.9 (CH), 136.6 (CH), 133.5 (CH),

131.1 (C), 129.6 (CH), 127.3 (CH), 123.5 (CH), 121.9 (CH), 118.8 (C), 118.6 (CH), 109.6 (CN), 109.5 (C3), 61.6 (C6), 43.4 (C5), 38.7 (C4), 28.2 (C5a,b), 24.0 (CH<sub>3</sub>). FTIR (KBr): 3064, 3047, 3018, 2961, 2930, 2877, 2856, 2229, 1617, 1583, 1565, 1550, 1498, 1490, 1481, 1468, 1442, 1431, 1407, 1391, 1372, 1350, 1324, 1307, 1296, 1278, 1255, 1246, 1209, 1181, 1156, 1147, 1123, 1085, 1079, 1001, 988. HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> Calcd. for C<sub>24</sub>H<sub>22</sub>N<sub>5</sub>: 380.1870. Found: 380.1872.

**4-(5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)quinoline-6-carboxamide (8i).** **8h** (50 mg, 0.132 mmol) was dissolved in DMSO (0.5 mL), K<sub>2</sub>CO<sub>3</sub> (3.9 mg, 0.029 mmol, 0.2 equiv.) was added and finally 30% aq. H<sub>2</sub>O<sub>2</sub> (18 µL, 0.173 mmol, 1.3 equiv.) in H<sub>2</sub>O (25 µL) was added dropwise (gently exothermic). The solution was stirred for 3 h at rt and Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (13 mg) in H<sub>2</sub>O (0.4 mL) was added. Solvents were evaporated and the crude product was purified by preparative HPLC (MeCN/H<sub>2</sub>O/CF<sub>3</sub>COOH) and lyophilized to get 62 mg, 92% of light yellow solid as trifluoroacetate salt; mp 98.1–99.3 °C. <sup>1</sup>H NMR (CD<sub>3</sub>CN): δ<sub>H</sub> 9.10 (d, <sup>3</sup>*J* = 5.6, 1H, CH), 8.55 (s, 1H, CH), 8.40–8.50 (m, 2H, 2×CH), 7.99 (t, <sup>3</sup>*J* = 8.0, 1H, CH), 7.88 (d, <sup>3</sup>*J* = 5.6, 1H, CH), 7.65 (bs, 1H, NH<sub>2</sub>), 7.63 (d, <sup>3</sup>*J* = 7.9, 1H, CH), 7.25 (d, <sup>3</sup>*J* = 7.9, 1H, CH), 6.54 (bs, 1H, NH<sub>2</sub>), 4.12 (s, 2H, H6), 2.80 (s, 2H, H4), 2.79 (s, 3H, CH<sub>3</sub>), 1.33 (s, 6H, H5a,b). <sup>13</sup>C {<sup>1</sup>H} NMR (CD<sub>3</sub>CN): δ<sub>C</sub> 167.8 (O=C-NH<sub>2</sub>), 160.9 (q, <sup>2</sup>*J*<sub>C,F</sub> = 37.3, CF<sub>3</sub>C=O), 156.9 (C), 151.1 (C), 150.7 (C), 146.8 (CH), 146.6 (CH), 145.5 (C), 145.4 (C), 141.8 (C), 135.0 (C), 133.9 (CH), 127.8 (CH), 127.7 (CH), 127.7 (C), 124.7 (CH), 124.5 (CH), 123.4 (CH), 117.0 (q, <sup>1</sup>*J*<sub>C,F</sub> = 289.5, CF<sub>3</sub>), 111.5 (C3), 62.6 (C6), 44.6 (C5), 39.4 (C4), 27.7 (C5a,b), 20.1 (CH<sub>3</sub>). FTIR (KBr): 3418, 3194, 3098, 2966, 2936, 2878, 1776, 1678, 1632, 1626, 1559, 1492, 1454,



1429, 1382, 1320, 1270, 1201, 1180, 1141, 967. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{24}H_{24}N_5O$ : 398.1975. Found: 398.1978.

**3-(2-Chloropyridin-4-yl)-5,5-dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-**

**pyrrolo[1,2-*b*] pyrazole (8j).** Column chromatography (EtOAc/DCM 1:1) afforded 72 mg, 48% of an off-white solid; mp 124.5–126.1 °C.  $^1H$  NMR ( $CDCl_3$ ):  $\delta_H$  8.16 (d,  $^3J = 5.3$ , 1H, CH), 7.53 (t,  $^3J = 7.7$ , 1H, CH), 7.34 (d,  $^3J = 7.7$ , 1H, CH), 7.29 (d,  $^3J = 1.5$ , 1H, CH), 7.06 (d,  $^3J = 7.7$ , 1H, CH), 7.04 (dd,  $^3J = 5.3$ , 1.5, 1H, CH), 3.94 (s, 2H, H6), 2.83 (s, 2H, H4), 2.47 (s, 3H, CH<sub>3</sub>), 1.30 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR ( $CDCl_3$ ):  $\delta_C$  158.3 (C), 152.5 (C), 151.7 (C), 151.2 (C), 148.9 (CH), 145.8 (C), 144.9 (C), 136.8 (CH), 123.0 (CH), 122.5 (CH), 121.7 (CH), 120.0 (CH), 111.3 (C3), 61.2 (C6), 43.2 (C5), 39.4 (C4), 28.2 (C5a,b), 24.3 (CH<sub>3</sub>). FTIR (neat): 3059, 2959, 2927, 2872, 2854, 1592, 1551, 1529, 1492, 1466, 1429, 1408, 1389, 1374, 1358, 1321, 1311, 1181, 1159, 1146, 1122, 1086, 999, 990. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{19}H_{20}N_4Cl$ : 339.1371. Found: 339.1372.

**4-((4-(5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-**

**yl)pyridin-2-yl)amino)benzenesulfonamide (8k).** **8j** (50 mg, 0.148 mmol), sulfanilamide (51 mg, 0.295 mmol, 2 equiv.),  $CS_2CO_3$  (144 mg, 0.443 mmol, 3 equiv.),  $Pd(OAc)_2$  (3.3 mg, 0.015 mmol, 10 mol%) and Xantphos (8.5 mg, 0.015 mmol, 10 mol%) were dissolved in anhydrous DMF (2.5 mL). The reaction mixture was stirred at 150 °C under an argon atmosphere. After 1 h the reaction mixture was cooled down and solvent was evaporated. The residue was dissolved in MeOH (5 mL) and filtered over a short pad of celite and washed with MeOH (2×15 mL). Solvent was evaporated and the crude product was purified by preparative HPLC (MeCN/ $H_2O$ / $CF_3COOH$ ) to get 70 mg, 81% of

light yellow solid as trifluoroacetate salt; mp 79.6–82.2 °C.  $^1\text{H}$  NMR (MeOD- $d_4$ ):  $\delta_{\text{H}}$  8.31 (t,  $^3J = 8.0$ , 1H, CH), 8.00 (d,  $^3J = 7.0$ , 1H, CH), 7.87–7.91 (m, 2H, 2×CH), 7.81 (d,  $^3J = 7.9$ , 1H, CH), 7.77 (d,  $^3J = 7.9$ , 1H, CH), 7.44–7.48 (m, 2H, 2×CH), 7.05 (dd,  $^3J = 6.6$ , 1.7, 1H, CH), 6.97 (d,  $^3J = 1.1$ , 1H, CH), 4.11 (s, 2H, H<sub>6</sub>), 3.05 (s, 2H, H<sub>4</sub>), 2.76 (s, 3H, CH<sub>3</sub>), 1.38 (s, 6H, H<sub>5a,b</sub>).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (MeOD- $d_4$ ):  $\delta_{\text{C}}$  160.4 (q,  $^2J_{\text{C,F}} = 36.6$ , CF<sub>3</sub>C=O), 157.3 (C), 153.2 (C), 150.2 (C), 149.4 (C), 147.4 (C), 146.6 (C), 146.1 (CH), 142.2 (C), 141.5 (C), 139.6 (CH), 129.1 (2×CH), 127.8 (CH), 125.1 (CH), 123.9 (2×CH), 115.4 (CH), 114.6 (q,  $^1J_{\text{C,F}} = 284.3$ , CF<sub>3</sub>), 113.5 (C<sub>3</sub>), 110.9 (CH), 62.5 (C<sub>6</sub>), 44.7 (C<sub>5</sub>), 40.1 (C<sub>4</sub>), 27.9 (C<sub>5a,b</sub>), 20.5 (CH<sub>3</sub>). FTIR (KBr): 3425, 3260, 3069, 2965, 2934, 2878, 1760, 1679, 1646, 1592, 1501, 1470, 1434, 1412, 1394, 1374, 1337, 1276, 1202, 1183, 1162, 1101, 1039, 989. HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> Calcd. for C<sub>25</sub>H<sub>27</sub>N<sub>6</sub>O<sub>2</sub>S: 475.1911. Found: 475.1911.

**Pyridin-2-yl and 6-Methylpyridin-2-yl Substituted Products at C2: Deprotection of *N*-oxides.** Relevant ***N*-oxide** (105 mg, SI), ammonium formate (10 equiv.) and 5% Pd/C (10 mol%) were mixed in anhydrous MeOH (5 mL). The suspension was refluxed under an argon atmosphere for 1-2 h. The mixture was filtered and the solid part was washed with MeOH (2×5 mL). MeOH was evaporated, water was added (10 mL) and the product was extracted with DCM (2×10 mL). The organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The crude product was purified by crystallization from MeCN. Spectral characteristics of products **7d** (86%)/**8b** (88%) and **7l** (90%)/**8e** (91%) obtained after deprotection of respective *N*-oxides correspond to those recorded after C-H activation/functionalization sequence.

**3-(4-Methoxyphenyl)-5,5-dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (7r).** **7r-*N*-oxide** (0.313 mmol), ammonium formate (197 mg, 3.13 mmol), 5% Pd/C (67 mg, 0.031 mmol) in anhydrous MeOH were refluxed for 1 h. Crystallization afforded 90 mg, 90% of a colorless solid; mp 128.8–129.7 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.58–8.61 (m, 1H, CH), 7.49–7.56 (m, 1H, CH), 7.38–7.41 (m, 1H, CH), 7.17 (d,  $^3J = 8.6$ , 2H, 2×CH), 7.09–7.14 (m, 1H, CH), 6.82 (d,  $^3J = 8.6$ , 2H, 2×CH), 3.96 (s, 2H, H6), 3.77 (s, 3H,  $\text{OCH}_3$ ), 2.77 (s, 2H, H4), 1.30 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  158.1 (C), 153.2 (C), 151.3 (C), 149.6 (CH), 144.3 (C), 135.9 (CH), 129.8 (2×CH), 126.0 (C), 122.9 (CH), 122.0 (CH), 114.5 (C3), 113.8 (2×CH), 61.2 (C6), 55.2 ( $\text{OCH}_3$ ), 43.1 (C5), 39.0 (C4), 28.3 (C5a,b). FTIR (neat): 2983, 2956, 2925, 2881, 2836, 1588, 1553, 1508, 1495, 1458, 1445, 1414, 1403, 1323, 1301, 1291, 1242, 1178, 1140, 1125, 1014, 994. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}$ : 320.1757. Found: 320.1754.

**3-(4-Methoxyphenyl)-5,5-dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole (8l).** **8l-*N*-oxide** (0.300 mmol), ammonium formate (189 mg, 3.00 mmol), 5% Pd/C (64 mg, 0.030 mmol) in anhydrous MeOH were refluxed for 2 h. Crystallization afforded 98 mg, 98% of a colorless solid; mp 139.0–139.4 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.38 (t,  $^3J = 7.7$ , 1H, CH), 7.16 (d,  $^3J = 8.4$ , 2H, 2×CH), 7.09 (d,  $^3J = 7.7$ , 1H, CH), 6.98 (d,  $^3J = 7.7$ , 1H, CH), 6.80 (d,  $^3J = 8.4$ , 2H, 2×CH), 3.96 (s, 2H, H6), 3.75 (s, 3H,  $\text{OCH}_3$ ), 2.75 (s, 2H, H4), 2.56 (s, 3H,  $\text{CH}_3$ ), 1.28 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  158.5 (CH), 158.0 (C), 152.4 (C), 151.6 (C), 144.0 (C), 136.0 (C), 129.8 (2×CH), 126.1 (C), 121.6 (CH), 120.3 (CH), 114.4 (C3), 113.7 (2×CH), 61.2 (C6), 55.2 ( $\text{OCH}_3$ ), 43.0 (C5), 38.9 (C4), 28.3 (C5a,b), 24.7 ( $\text{CH}_3$ ). FTIR (neat): 2997, 2952, 2925, 2883, 2840, 1587, 1577, 1548,

1504, 1481, 1458, 1446, 1422, 1399, 1389, 1332, 1302, 1288, 1261, 1242, 1179, 1158, 1127, 1089, 1031, 1016, 993. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{21}H_{23}N_3O$ : 334.1914. Found: 334.1909.

**Pyridin-2-yl and 6-Methylpyridin-2-yl Substituted Products at C2: Demethylation of methoxy group.** **7r** or **8l** (60 mg) was dissolved in anhydrous DCM (4 mL) under an argon atmosphere. The mixture was cooled down to  $-78\text{ }^{\circ}\text{C}$  and 1 M  $\text{BBr}_3$  in DCM (2.5 equiv.) was added dropwise. The solution was stirred for 30 min, then it was left to heat up to rt and stirred for 20 h. DCM (4 mL) was added, the reaction was quenched with sat.  $\text{NaHCO}_3$  (2 mL) and the mixture was stirred for 30 min. The organic phase was separated and water phase was extracted with DCM (3 $\times$ 7 mL). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and evaporated. The crude product was crystallized (MeOH, **7s**) or purified by column chromatography (MeOH/EtOAc 1:2, **8m**).

**4-(5,5-Dimethyl-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)phenol (7s).**

Crystallization afforded 54 mg, 95% of a colorless solid; mp  $138.5\text{--}140.2\text{ }^{\circ}\text{C}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.60–8.65 (m, 1H, CH), 7.67–7.75 (m, 1H, CH), 7.60–7.65 (m, 1H, CH), 7.22–7.31 (m, 1H, CH), 6.99 (d,  $^3J = 8.4$ , 2H, 2 $\times$ CH), 6.62 (d,  $^3J = 8.4$ , 2H, 2 $\times$ CH), 3.98 (s, 2H, H6), 2.80 (s, 2H, H4), 1.34 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  155.5 (C), 153.4 (C), 150.8 (C), 148.9 (CH), 144.5 (C), 137.0 (CH), 129.5 (2 $\times$ CH), 124.5 (C), 123.7 (CH), 122.6 (CH), 115.9 (2 $\times$ CH), 115.2 (C3), 61.3 (C6), 43.1 (C5), 39.0 (C4), 28.4 (C5a,b). FTIR (neat): 3314, 3057, 2955, 2927, 2902, 2870, 2806, 2667, 1616, 1595, 1558, 1514, 1502, 1461, 1443, 1410, 1367, 1319, 1300, 1276, 1262, 1235, 1178, 1151, 1090, 1035, 1004, 989. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{19}H_{19}N_3O$ : 306.1601. Found: 306.1598.

**4-(5,5-Dimethyl-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)phenol (8m).** Column chromatography afforded 49 mg, 85% of a colorless solid; mp 214.6–215.9 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.40 (t,  $^3J = 7.7$ , 1H, CH), 7.12 (d,  $^3J = 7.7$ , 1H, CH), 7.00 (d,  $^3J = 7.7$ , 1H, CH), 6.94–6.99 (m, 2H, 2 $\times$ CH), 6.64–6.70 (m, 2H, 2 $\times$ CH), 3.90 (s, 2H, H6), 2.70 (s, 2H, H4), 2.51 (s, 3H,  $\text{CH}_3$ ), 1.24 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  158.4 (C), 155.5 (C), 152.3 (C), 151.2 (C), 144.1 (C), 136.5 (CH), 129.6 (2 $\times$ CH), 124.5 (C), 122.0 (CH), 120.8 (CH), 115.7 (2 $\times$ CH), 115.0 (C3), 61.1 (C6), 43.0 (C5), 39.0 (C4), 28.3 (C5a,b), 24.3 ( $\text{CH}_3$ ). FTIR (KBr): 3458, 3071, 3017, 2957, 2926, 2872, 2806, 1615, 1589, 1577, 1555, 1511, 1482, 1463, 1441, 1370, 1329, 1289, 1265, 1239, 1184, 1177, 1162, 1091, 1005, 996. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}$ : 320.1757. Found: 320.1758.

**Pyridin-2-yl and 6-Methylpyridin-2-yl Substituted Products at C2: N-oxides 9a,b. 3d**

(500 mg, 2.34 mmol) or **3e** (500 mg, 2.20 mmol) was dissolved in anhydrous DCM (10 mL) and the solution was cooled down to 0 °C. *m*-Chloroperoxybenzoic acid (1.5 equiv., 3.51 mmol (**3d**), 3.30 mmol (**3e**)) was added slowly in few portions. The mixture was left to heat up to room temperature and stirred for 20 h under an argon atmosphere. The reaction was quenched with sat. aq.  $\text{NaHCO}_3$  (7 mL + 7 mL  $\text{H}_2\text{O}$ ) and stirred for next 15 min. The water phase was extracted with DCM (2 $\times$ 10 mL), combined organic phases were washed with brine (10 mL), dried over  $\text{MgSO}_4$  and filtered. DCM was evaporated and the crude product was purified by column chromatography (MeOH/EtOAc 1:5).

Procedure for **6b** and **6d** oxidation leading to **9c** and **9d** is the same as described above. It is up to researcher which procedure is going to be followed since both produced comparable results.

**2-(5,5-Dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)pyridine-1-oxide (9a).** Yield: 452 mg, 84 % of light yellow solid; mp 98.1–99.0 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.24–8.30 (m, 1H, CH), 8.11–8.18 (m, 1H, CH), 7.39 (s, 1H, CH), 7.21–7.29 (m 1H, CH), 7.08–7.16 (m, 1H, CH), 3.95 (s, 2H, H6), 2.77 (s, 2H, H4), 1.32 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  147.1 (C), 145.8 (CH), 143.9 (C), 140.6 (C), 125.4 (CH), 124.6 (CH), 123.4 (CH), 103.6 (C3), 61.4 (C6), 43.3 (C5), 38.9 (C4), 28.2 (C5a,b). FTIR (neat): 3077, 3034, 2979, 2960, 2923, 2868, 2850, 1604, 1536, 1508, 1481, 1453, 1437, 1404, 1390, 1370, 1350, 1328, 1268, 1188, 1161, 1147, 1129, 1057, 1034. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}$ : 230.1288. Found: 230.1291.

**2-(5,5-Dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)-6-methylpyridine-1-oxide (9b).** Yield: 471 mg, 88 % of colorless solid; mp 113.9–114.9 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.00 – 8.05 (m, 1H, CH), 7.37 – 7.38 (m, 1H, CH), 7.10 – 7.16 (m, 2H, 2 $\times$ CH), 3.91 (s, 2H, H6), 2.74 (s, 2H, H4), 2.54 (s, 3H,  $\text{CH}_3$ -Ar), 1.28 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  149.7 (C), 147.7 (C), 145.6 (C), 143.8 (C), 124.7 (CH), 123.9 (CH), 122.2 (CH), 103.5 (C3), 61.4 (C6), 43.3 (C5), 38.9 (C4), 28.2 (C5a,b), 18.5 ( $\text{CH}_3$ -Ar). FTIR (neat): 3171, 3072, 3043, 2957, 2924, 2870, 1564, 1536, 1509, 1482, 1464, 1447, 1424, 1398, 1388, 1378, 1370, 1327, 1259, 1222, 1206, 1177, 1157, 1095, 1074, 1038, 976. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}$ : 244.1444. Found: 244.1445.

**Pyridin-2-yl and 6-Methylpyridin-2-yl Substituted Products at C2: Bromination to 9c,d.**

**9a** (500 mg, 2.18 mmol) or **9b** (500 mg, 2.05 mmol) was dissolved in anhydrous  $\text{CHCl}_3$  (15 mL) and *N*-bromosuccinimide (1.2 equiv., 2.62 mmol (**9a**), 2.47 mmol (**9b**)) was added in few portions. The reaction mixture was stirred for 1 h at rt under an argon

atmosphere. DCM (15 mL) was added and the mixture was washed with 10% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (10 mL) and water (3×20 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by column chromatography (MeOH/EtOAc 1:4).

**2-(3-Bromo-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)pyridine-1-oxide**

**(9c).** Yield: 605 mg, 90 % of colorless solid; mp 175.2–176.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 8.32–8.36 (m, 1H, CH), 7.48–7.53 (m, 1H, CH), 7.23–7.33 (m, 2H, 2×CH), 3.99 (s, 2H, H<sub>6</sub>), 2.75 (s, 2H, H<sub>4</sub>), 1.35 (s, 6H, H<sub>5a,b</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 146.5 (C), 145.5 (C), 143.0 (C), 140.2 (CH), 128.6 (CH), 125.7 (CH), 124.7 (CH), 89.5 (C<sub>3</sub>), 62.5 (C<sub>6</sub>), 42.9 (C<sub>5</sub>), 38.4 (C<sub>4</sub>), 28.4 (C<sub>5a,b</sub>). FTIR (neat): 3099, 3081, 3048, 3030, 2969, 2954, 2939, 2867, 1544, 1510, 1487, 1442, 1415, 1387, 1371, 1353, 1320, 1260, 1244, 1178, 1166, 1111, 1097, 1010. Anal. Calcd. for C<sub>13</sub>H<sub>14</sub>N<sub>3</sub>OBr: C, 50.67; H, 4.58; N, 13.64. Found: C, 50.58; H, 4.53; N, 13.44.

**2-(3-Bromo-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)-6-methylpyridine-**

**1-oxide (9d).** Yield: 622 mg, 94 % of colorless solid; mp 136.6–137.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 7.37 (dd, <sup>3</sup>*J* = 7.7, 1.8, 1H, CH), 7.28 (dd, <sup>3</sup>*J* = 7.7, 1.8, 1H, CH), 7.14 (t, <sup>3</sup>*J* = 7.7, 1H, CH), 3.97 (s, 2H, H<sub>6</sub>), 2.73 (s, 2H, H<sub>4</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 1.33 (s, 6H, H<sub>5a,b</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 149.4 (C), 146.8 (C), 145.0 (C), 142.6 (C), 126.0 (CH), 125.9 (CH), 123.3 (CH), 89.0 (C<sub>3</sub>), 62.2 (C<sub>6</sub>), 42.7 (C<sub>5</sub>), 38.2 (C<sub>4</sub>), 28.2 (C<sub>5a,b</sub>), 18.1 (CH<sub>3</sub>). FTIR (neat): 2963, 2950, 2925, 2872, 1561, 1444, 1427, 1384, 1369, 1347, 1304, 1268, 1250, 1213, 1192, 1181, 1170, 1152, 1118, 1088, 1068, 1037, 992. Anal. Calcd. for C<sub>14</sub>H<sub>16</sub>N<sub>3</sub>OBr: C, 52.19; H, 5.01; N, 13.04. Found: C, 51.81; H, 5.02; N, 12.82.

**Pyridin-2-yl and 6-Methylpyridin-2-yl Substituted Products at C2: Suzuki cross-coupling reactions of brominated N-oxides.** **9c** or **9d** (250 mg) and other components were dissolved in DMF (4 mL) and the mixture was heated at 110 °C under an argon atmosphere. The reaction was stopped after 24 h, DMF was evaporated and the crude products were purified by column chromatography.

**2-(3-(4-Formylphenyl)-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)pyridine-1-oxide (7d-*N*-oxide).** **9c** (0.745 mmol), 4-formylphenylboronic acid (223 mg, 1.49 mmol, 2.0 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (86 mg, 0.075 mmol, 10 mol%), JohnPhos (45 mg, 0.149 mmol, 20 mol%) and 2 M aq. K<sub>2</sub>CO<sub>3</sub> (1.1 mL, 2.24 mmol, 3 equiv.) after column chromatography (MeOH/EtOAc 1:5) 184 mg, 74 % of colorless solid; mp 190.6–192.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 9.89 (s, 1H, HC=O), 8.26–8.33 (m, 2H, 2×CH), 7.56–7.63 (m, 1H, CH), 7.27–7.37 (m, 4H, 4×CH), 4.01 (s, 2H, H<sub>6</sub>), 2.96 (s, 2H, H<sub>4</sub>), 1.38 (s, 6H, H<sub>5a,b</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 191.8 (HC=O), 145.0 (C), 144.8 (C), 144.7 (C), 140.3 (CH), 140.1 (C), 134.2 (C), 130.2 (2×CH), 128.6 (CH), 126.5 (2×CH), 125.8 (CH), 125.5 (CH), 115.8 (C<sub>3</sub>), 61.6 (C<sub>6</sub>), 43.3 (C<sub>5</sub>), 39.9 (C<sub>4</sub>), 28.6 (C<sub>5a,b</sub>). FTIR (neat): 3078, 2959, 2928, 2872, 2852, 2735, 1696, 1605, 1569, 1553, 1501, 1491, 1461, 1440, 1419, 1390, 1371, 1306, 1268, 1256, 1216, 1169, 1133, 1096, 1043, 987. HRMS (ESI) *m/z*: [M + H]<sup>+</sup> Calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub>: 334.1550. Found: 334.1551.

**2-(3-(4-Formylphenyl)-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)-6-methylpyridine-1-oxide (8b-*N*-oxide).** **9d** (0.715 mmol), 4-formylphenylboronic acid (214 mg, 1.43 mmol, 2.0 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (83 mg, 0.072 mmol, 10 mol%), JohnPhos (43 mg, 0.143 mmol, 20 mol%) and 2 M aq. K<sub>2</sub>CO<sub>3</sub> (1.1 mL, 2.15 mmol, 3 equiv.) afforded



after column chromatography (MeOH/EtOAc 1:5) 209 mg, 84 % of colorless solid; mp 241.1–242.5 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  9.91 (s, 1H, HC=O), 7.71–7.76 (m, 2H, 2 $\times$ CH), 7.41–7.47 (m, 1H, CH), 7.25–7.33 (m, 3H, 3 $\times$ CH), 7.15–7.21 (m, 1H, CH), 4.00 (s, 2H, H6), 2.98 (s, 2H, H4), 2.48 (s, 3H,  $\text{CH}_3$ ), 1.38 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  191.9 (HC=O), 149.8 (C), 145.8 (C), 144.6 (C), 140.3 (C), 134.0 (C), 130.2 (2 $\times$ CH), 126.4 (2 $\times$ CH), 126.2 (CH), 126.2 (CH), 124.0 (CH), 115.5 (C3), 61.5 (C6), 43.3 (C5), 40.1 (C4), 28.6 (C5a,b), 18.5 ( $\text{CH}_3$ ). FTIR (neat): 3056, 2961, 2925, 2887, 2870, 2851, 2825, 2734, 1693, 1668, 1604, 1571, 1562, 1500, 1489, 1462, 1447, 1433, 1392, 1385, 1362, 1320, 1307, 1270, 1257, 1217, 1184, 1166, 1112, 1098, 1075, 1039, 1018, 1010, 988. HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd. for  $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_2$ : 348.1707. Found: 348.1707.

**2-(5,5-Dimethyl-3-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)pyridine-1-oxide (7I-*N*-oxide). 9c** (0.745 mmol), 4-pyridynylboronic acid (183 mg, 1.49 mmol, 2.0 equiv.),  $\text{Pd}(\text{PPh}_3)_4$  (86 mg, 0.075 mmol, 10 mol%), JohnPhos (45 mg, 0.149 mmol, 20 mol%) and 2 M aq.  $\text{K}_2\text{CO}_3$  (1.1 mL, 2.24 mmol, 3 equiv.) afforded after column chromatography (MeOH/EtOAc 1:2) 135 mg, 59 % of colorless solid; mp 232.8–234.6°C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  8.41–8.47 (m, 2H, 2 $\times$ CH), 8.27–8.32 (m, 1H, CH), 7.54–7.59 (m, 1H, CH), 7.30–7.35 (m, 2H, 2 $\times$ CH), 7.03–7.06 (m, 2H, 2 $\times$ CH), 4.00 (s, 2H, H6), 2.97 (s, 2H, H4), 1.38 (s, 6H, H5a,b).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  149.5 (2 $\times$ CH), 145.2 (C), 145.1 (C), 144.5 (C), 141.6 (C), 140.2 (CH), 128.7 (CH), 126.0 (CH), 125.5 (CH), 120.8 (2 $\times$ CH), 114.2 (C3), 61.5 (C6), 43.3 (C5), 40.0 (C4), 28.6 (C5a,b). FTIR (neat): 3071, 3027, 2959, 2926, 2872, 2852, 1602, 1560, 1508, 1491, 1461, 1439, 1418, 1391, 1371, 1309,

1269, 1257, 1221, 1182, 1135, 1086, 1043, 1002, 990. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{18}H_{19}N_4O$ : 307.1553. Found: 307.1555.

**2-(5,5-Dimethyl-3-(pyridin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)-6-**

**methypyridine-1-oxide (8e-*N*-oxide). 9d** (0.715 mmol), 4-pyridynylboronic acid (176 mg, 1.43 mmol, 2.0 equiv.),  $Pd(PPh_3)_4$  (83 mg, 0.072 mmol, 10 mol%), JohnPhos (43 mg, 0.143 mmol, 20 mol%) and 2 M aq.  $K_2CO_3$  (1.1 mL, 2.15 mmol, 3 equiv.) afforded after column chromatography (EtOAc/MeOH 5:1) 137 mg, 60 % of colorless solid; mp 228.2–229.6 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H$  8.37–8.42 (m, 2H, 2 $\times$ CH), 7.38–7.42 (m, 1H, CH), 7.27–7.33 (m, 1H, CH), 7.13–7.19 (m, 1H, CH), 6.94–7.02 (m, 2H, 2 $\times$ CH), 3.97 (s, 2H, H6), 2.96 (s, 2H, H4), 2.48 (s, 3H,  $CH_3$ ), 1.36 (s, 6H, H5a,b).  $^{13}C$   $\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta_C$  149.9 (2 $\times$ CH), 149.8 (C), 145.9 (C), 144.8 (C), 144.3 (C), 141.2 (C), 126.3 (CH), 126.1 (CH), 124.0 (CH), 120.5 (2 $\times$ CH), 113.9 (C3), 61.4 (C6), 43.2 (C5), 40.1 (C4), 28.5 (C5a,b), 18.3 ( $CH_3$ ). FTIR (neat): 3089, 3059, 3038, 2986, 2956, 2937, 2927, 2914, 2884, 2870, 1606, 1566, 1543, 1499, 1490, 1463, 1447, 1432, 1406, 1392, 1385, 1380, 1362, 1328, 1317, 1307, 1268, 1261, 1255, 1223, 1206, 1185, 1128, 1095, 1067, 1023, 996, 991. HRMS (ESI)  $m/z$ :  $[M + H]^+$  Calcd. for  $C_{19}H_{21}N_4O$ : 321.1710. Found: 321.1711.

**2-(3-(4-Methoxyphenyl)-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-**

**yl)pyridine-1-oxide (7r-*N*-oxide). 9c** (0.745 mmol), 4-methoxyphenylboronic acid (283 mg, 1.86 mmol, 2.5 equiv.),  $Pd(PPh_3)_4$  (86 mg, 0.075 mmol, 10 mol%), JohnPhos (45 mg, 0.149 mmol, 20 mol%) and 2 M aq.  $K_2CO_3$  (1.1 mL, 2.24 mmol, 3 equiv.) afforded after column chromatography (MeOH/EtOAc 1:5) 212 mg, 85 % of light yellow solid; mp 179.3–180.4 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H$  8.21–8.28 (m, 1H, CH), 7.41–7.51 (m, 1H,

CH), 7.15–7.28 (m, 2H, 2×CH), 7.09 (d,  $^3J = 8.6$ , 2H, 2×CH), 6.78 (d,  $^3J = 8.6$ , 2H, 2×CH), 3.98 (s, 2H, H6), 3.74 (s, 3H, OCH<sub>3</sub>), 2.89 (s, 2H, H4), 1.35 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  158.1 (C), 145.1 (C), 144.3 (C), 143.3 (C), 140.1 (CH), 128.9 (CH), 127.6 (2×CH), 125.9 (C), 125.3 (CH), 124.8 (CH), 116.3 (C3), 114.1 (2×CH), 61.4 (C6), 55.2 (OCH<sub>3</sub>), 43.1 (C5), 39.6 (C4), 28.6 (C5a,b). FTIR (neat): 3071, 2961, 2927, 2872, 2840, 1612, 1553, 1504, 1464, 1438, 1417, 1370, 1327, 1298, 1288, 1242, 1182, 1132, 1091, 1031, 1013, 986. HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> Calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: 336.1706. Found: 336.1711.

**2-(3-(4-Methoxyphenyl)-5,5-dimethyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl)-6-**

**methylpyridine-1-oxide (8I-*N*-oxide). 9d** (0.715 mmol), 4-methoxyphenylboronic acid (272 mg, 1.79 mmol, 2.5 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (83 mg, 0.072 mmol, 10 mol%), JohnPhos (43 mg, 0.143 mmol, 20 mol%) and 2 M aq. K<sub>2</sub>CO<sub>3</sub> (1.1 mL, 2.15 mmol, 3 equiv.) afforded after column chromatography (MeOH/EtOAc 1:6) 207 mg, 83 % of colorless solid; mp 177.0–177.9 °C.  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  7.31 (d,  $^3J = 7.7$ , 1H, CH), 7.25 (d,  $^3J = 7.7$ , 1H, CH), 7.10 (t,  $^3J = 7.7$ , 1H, CH), 7.05–7.10 (m, 2H, 2×CH), 6.75–6.81 (m, 2H, 2×CH), 3.98 (s, 2H, H6), 3.75 (s, 3H, OCH<sub>3</sub>), 2.89 (s, 2H, H4), 2.48 (s, 3H, CH<sub>3</sub>), 1.35 (s, 6H, H5a,b).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  157.7 (C), 149.6 (C), 144.8 (C), 144.6 (C), 142.8 (C), 127.5 (2×CH), 126.3 (CH), 125.8 (CH), 125.7 (CH), 124.1 (C), 115.9 (C3), 113.8 (2×CH), 61.1 (C6), 55.0 (OCH<sub>3</sub>), 42.9 (C5), 39.4 (C4), 28.4 (C5a,b), 18.3 (CH<sub>3</sub>). FTIR (neat): 3001, 2954, 2931, 2882, 2830, 1616, 1561, 1504, 1463, 1445, 1431, 1390, 1377, 1357, 1326, 1302, 1290, 1260, 1241, 1174, 1033, 1018, 987. HRMS (ESI)  $m/z$ : [M + H]<sup>+</sup> Calcd. for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: 350.1863. Found: 350.1857.

## Associated Content

Supporting Information

Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, crystal structures and kinase inhibition data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## Author Contributions

L.T. carried out experimental work and compiled characterization data. J.G. wrote the manuscript. E.R. and V.K. measured biochemical activities. M.P. conceived and coordinated the work. All authors have given approval to the final version of the manuscript.

## Notes

The authors declare no competing financial interest.

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